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Comments and Controversies: Multiplex Genetic Testing for Cancer Susceptibility: Out on the High Wire Without a Net? *S.M. Domchek et al*

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Effects of Melatonin on Appetite and Other Symptoms in Patients With Advanced Cancer and Cachexia: A Double-Blind Placebo-Controlled Trial

Egidio Del Fabbro, Rony Dev, David Hui, et al

pp 1271-1276

Purpose: Prior studies have suggested that melatonin, a frequently used integrative medicine, can attenuate weight loss, anorexia, and fatigue in patients with cancer. These studies were limited by a lack of blinding and absence of placebo controls. The primary purpose of this study was to compare melatonin with placebo for appetite improvement in patients with cancer cachexia.
Patients and Methods: We performed a randomized, double-blind, 28-day trial of melatonin 20 mg versus placebo in patients with advanced lung or GI cancer, appetite scores ≥ 4 on a 0 to 10 scale (10 = worst appetite), and history of weight loss $\geq 5\%$. Assessments included weight, symptoms by the Edmonton Symptom Assessment Scale, and quality of life by the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Differences between groups from baseline to day 28 were analyzed using one-sided, two-sample *t* tests or Wilcoxon two-sample tests. Interim analysis halfway through the trial had a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule. Decision boundaries were to accept the null hypothesis of futility if the test statistic $z < 0.39$ ($P \geq .348$) and reject the null hypothesis if $z > 2.54$ ($P \leq .0056$).
Results: After interim analysis of 48 patients, the study was closed for futility. There were no significant differences between groups for appetite ($P = .78$) or other symptoms, weight ($P = .17$), FAACT score ($P = .95$), toxicity, or survival from baseline to day 28.
Conclusion: In cachectic patients with advanced cancer, oral melatonin 20 mg at night did not improve appetite, weight, or quality of life compared with placebo.
J Clin Oncol 31:1271-1276.

■ ■ ■

Sex Differences in the Return-to-Work Process of Cancer Survivors 2 Years After Diagnosis: Results From a Large French Population-Based Sample

Patricia Marino, Luis Sagaon Teyssier, Laetitia Malavolti, et al

pp 1277-1284

Purpose: To investigate the effects of clinical, sociodemographic, and occupational factors on time to return to work (RTW) during the 2 years after cancer diagnosis and to analyze whether sex differences exist.
Patients and Methods: This study was based on a French national cross-sectional survey involving 4,270 cancer survivors. Time to RTW was estimated through the duration of sick leave of 801 cancer survivors younger than 58 years who were employed during the 2-year survey. Multivariate analysis of the RTW after sick leave was performed using a Weibull accelerated failure time model.
Results: We found some sex differences in the RTW process. Older men returned to work more slowly than older women ($P = .013$), whereas married men returned to work much faster than married women ($P = .019$). Duration dependence was also sex-specific. In men, the time spent on sick leave was independent of the probability of returning to work, whereas in women, this duration dependence was positive ($P < .001$). For both men and women, clinical factors including chemotherapy, adverse effects, and cancer severity were found to delay RTW ($P = .035$, $P = .001$, and $P < .001$, respectively). Survivors investing most strongly in their personal lives also delayed their RTW ($P = .006$), as did those with a permanent work contract ($P = .042$). The factor found to accelerate RTW was a higher educational level ($P = .014$).
Conclusion: The RTW process 2 years after cancer diagnosis differed between men and women. A better knowledge of this process should help the national implementation of more cost-effective strategies for managing the RTW of cancer survivors.
J Clin Oncol 31:1277-1284.

■ ■ ■

Effect of Ruxolitinib Therapy on Myelofibrosis-Related Symptoms and Other Patient-Reported Outcomes in COMFORT-I: A Randomized, Double-Blind, Placebo-Controlled Trial

Ruben A. Mesa, Jason Gotlib, Vikas Gupta, et al

pp 1285-1292

Purpose: To assess the effects of ruxolitinib on symptom burden and quality of life (QoL) and to evaluate the ability of the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 to measure meaningful changes in myelofibrosis-related symptoms in patients with myelofibrosis.

Patients and Methods: COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment-I) is a double-blind, placebo-controlled phase III study evaluating ruxolitinib in patients with intermediate-2 or high-risk myelofibrosis. Exploratory analyses were conducted on the following patient-reported outcomes (PROs) assessments: modified MFSAF v2.0 (individual symptoms and Total Symptom Score [TSS]), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale, and Patient Global Impression of Change (PGIC).

Results: Patients receiving ruxolitinib experienced improvements in individual myelofibrosis-related symptoms, although patients receiving placebo experienced worsening ($P < .001$). The majority (91%) of ruxolitinib-treated patients designated as ≥ 50% TSS responders (≥ 50% TSS improvement) self-reported their condition as either "Much improved" or "Very much improved" on the PGIC. These patients achieved significant improvements in the EORTC QLQ-C30 functional domains and Global Health Status/QoL versus patients receiving placebo, who experienced worsening on these measures ($P \leq .0135$). Ruxolitinib-treated patients with a lesser degree of symptom improvement (< 50% TSS responders) also achieved improvements over placebo on these measures. The degree of spleen volume reduction with ruxolitinib correlated with improvements in TSS, PGIC, PROMIS Fatigue Scale, and EORTC Global Health Status/QoL. Ruxolitinib-treated patients who achieved a ≥ 35% reduction in spleen volume experienced the greatest improvements in these PROs.

Conclusion: Ruxolitinib-treated patients achieved clinically meaningful improvements in myelofibrosis-related symptoms and QoL, but patients receiving placebo reported worsening of symptoms and other PROs.

J Clin Oncol 31:1285-1292.

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Curability of Patients With Acute Myeloid Leukemia Who Did Not Undergo Transplantation in First Remission

Alan K. Burnett, Anthony Goldstone, Robert K. Hills, et al

pp 1293-1301

Purpose: The aims of this study were to quantify the prospects of salvage treatment of patients who did not undergo transplantation in first complete remission (CR1) and to assess the contribution of allograft in second complete remission (CR2) with respect to major risk groups. This evaluation can inform the decision whether to offer a transplant in CR1.

Patients and Methods: Of 8,909 patients who entered the Medical Research Council AML10, AML12, and AML15 trials, 1,271 of 3,919 patients age 16 to 49 years who did not receive a transplant in CR1 relapsed. Of these patients, 19% are alive beyond 5 years compared with 7% of patients who relapsed after an allograft in CR1. Overall survival and the contribution of a transplant in CR2 were assessed overall and by cytogenetic risk group by using Mantel-Byar analysis.

Results: Fifty-five percent of patients who relapsed entered CR2. This percentage varied by risk group as follows: favorable (82%), intermediate (54%), adverse (27%), and unknown (53%), which resulted in 5-year survivals of 32%, 17%, 7%, and 23%, respectively. Sixty-seven percent of remitters received an allotransplant that delivered superior survival compared with patients who did not receive a stem-cell transplant (42% *v* 16%). A more-stringent assessment of a transplant by using delayed-entry (Mantel-Byar) analysis confirmed the benefit of transplant overall and within intermediate and adverse risk groups but not the favorable subgroup.

Conclusion: Successful salvage treatment of patients who do not undergo transplantation in CR1 and relapse can be achieved in 19% of patients, which is improved by a transplant except in favorable risk disease. This result suggests that, for intermediate-risk patients in particular, equivalent overall survival can be achieved by delaying transplantation until after relapse, which would require many fewer transplants.

J Clin Oncol 31:1293-1301.

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Post-Transplantation Lymphoproliferative Disorder After Kidney Transplantation: Report of a Nationwide French Registry and the Development of a New Prognostic Score

Sophie Caillard, Raphael Porcher, François Provot, et al

pp 1302-1309

Purpose: Post-transplantation lymphoproliferative disorder (PTLD) is associated with significant mortality in kidney transplant recipients. We conducted a prospective survey of the occurrence of PTLD in a French nationwide population of adult kidney recipients over 10 years.

Patients and Methods: A French registry was established to cover a nationwide population of transplant recipients and prospectively enroll all adult kidney recipients who developed PTLD between January 1, 1998, and December 31, 2007. Five hundred patient cases of PTLD were referred to the French registry. The prognostic factors for PTLD were investigated using Kaplan-Meier and Cox analyses.

Results: Patients with PTLD had a 5-year survival rate of 53% and 10-year survival rate of 45%. Multivariable analyses revealed that age $>$ 55 years, serum creatinine level $>$ 133 μmol/L, elevated lactate dehydrogenase levels, disseminated lymphoma, brain localization, invasion of serous membranes, monomorphic PTLD, and T-cell PTLD were independent prognostic indicators of poor survival. Considering five variables at diagnosis (age, serum creatinine, lactate dehydrogenase, PTLD localization, and histology), we constructed a prognostic score that classified patients with PTLD as being at low, moderate, high, or very high risk for death. The 10-year survival rate was 85% for low-, 80% for moderate-, 56% for high-, and 0% for very high–risk recipients.

Conclusion: This nationwide study highlights the prognostic factors for PTLD and enables the development of a new prognostic score. After validation in an independent cohort, the use of this score should allow treatment strategies to be better tailored to individual patients in the future.

J Clin Oncol 31:1302-1309.

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T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

Asad Bashey, Xu Zhang, Connie A. Sizemore, et al

pp 1310-1316

Purpose: T-cell–replete grafts from haploidentical donors using post-transplantation cyclophosphamide may represent a solution for patients who require allogeneic hematopoietic cell transplantation (alloHCT) but lack a conventional donor. We compared outcomes of alloHCT using haploidentical donors with those of transplantation using conventional HLA-matched sibling donors (MRDs) and HLA-matched unrelated donors (MUDs).

Patients and Methods: Outcomes of 271 consecutive patients undergoing T-cell–replete first alloHCT for hematologic malignancies performed contemporaneously at a single center (53 using haploidentical donors; 117, MRDs; 101, MUDs) were compared. Overall and disease-free survival (DFS) were adjusted for effects of significant patient-, disease-, and transplantation-related covariates using a stratified Cox model.

Results: Patient characteristics were similar between the three donor groups. For patients undergoing MRD, MUD, and haploidentical transplantation, 24-month cumulative incidences of nonrelapse mortality were 13%, 16%, and 7% and of relapse were 34%, 34%, and 33%, respectively (*P* not significant [NS]). Cumulative incidences of grades 3 to 4 acute graft-versus-host disease (GVHD) at 6 months were 8%, 11%, and 11%, respectively (*P* NS); extensive chronic GVHD occurred in 54%, 54%, and 38% of patients, respectively ($P < .05$ for those undergoing haploidentical donor *v* MRD or MUD transplantation). Adjusted 24-month probabilities of survival were 76%, 67%, and 64% and of DFS were 53%, 52%, and 60%, respectively; these were not significantly different among the three donor groups.

Conclusion: Haploidentical transplantation performed using T-cell–replete grafts and post-transplantation cyclophosphamide achieves outcomes equivalent to those of contemporaneous transplantation performed using MRDs and MUDs. Such transplantation represents a valid alternative for patients who lack a conventional donor.

J Clin Oncol 31:1310-1316.

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Two-Year Randomized Controlled Prospective Trial Converting Treatment of Stable Renal Transplant Recipients With Cutaneous Invasive Squamous Cell Carcinomas to Sirolimus

Judith M. Hoogendijk-van den Akker, Paul N. Harden, Andries J. Hoitsma, et al

pp 1317-1323

Purpose: In light of the significant morbidity and mortality of cutaneous invasive squamous cell carcinomas (SCCs) in renal transplant recipients, we investigated whether conversion to sirolimus-based immunosuppression from standard immunosuppression could diminish the recurrence rate of these skin cancers.

Patients and Methods: In a 2-year randomized controlled trial, 155 renal transplant recipients with at least one biopsy-confirmed SCC were stratified according to age (< 55 *v* ≥ 55 years) and number of previous SCCs (one to nine *v* ≥ 10) and randomly assigned to conversion to sirolimus (n = 74) or continuation of their original immunosuppression (n = 81). Development of a new SCC within 2 years after random assignment was the primary end point.

Results: After 2 years of follow-up, the risk reduction of new SCCs in the multivariable analysis was not significant, with a hazard ratio (HR) of 0.76 (95% CI, 0.48 to 1.2; $P = .255$), compared with a non–sirolimus-based regimen. After the first year, there was a significant 50% risk reduction, with an HR of 0.50 (95% CI, 0.28 to 0.90; $P = .021$) for all patients together and an HR of 0.11 (95% CI, 0.01 to 0.94; $P = .044$) for patients with only one previous SCC. The tumor burden of SCC was reduced during the 2-year follow-up period in those receiving sirolimus (0.82 *v* 1.38 per year; HR, 0.51; 95% CI, 0.32 to 0.82; $P = .006$) if adjusted for the number of previous SCCs and age. Twenty-nine patients stopped taking sirolimus because of various adverse events.

Conclusion: Conversion to sirolimus-based immunosuppression failed to show a benefit in terms of SCC-free survival at 2 years.

J Clin Oncol 31:1317-1323.

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Lack of Specificity of Plasma Concentrations of Inhibin B and Follicle-Stimulating Hormone for Identification of Azoospermic Survivors of Childhood Cancer: A Report From the St Jude Lifetime Cohort Study

Daniel M. Green, Liang Zhu, Nan Zhang, et al

pp 1324-1328

Purpose: Many male survivors of childhood cancer are at risk for azoospermia. Although both the levels of follicle-stimulating hormone (FSH) and inhibin B are correlated with sperm concentration, their ability to predict azoospermia in survivors of childhood cancer remains uncertain.

Patients and Methods: Semen analysis was performed and serum levels of FSH and inhibin B were measured in 275 adult male survivors of childhood cancer who had received gonadotoxic therapy. Receiver operating characteristic (ROC) analysis was performed to determine the optimal inhibin B and FSH values for identifying patients with azoospermia. The patient sample was divided into a learning set and a validation set. Sensitivity, specificity, and positive and negative predictive value were calculated.

Results: Inhibin B was dichotomized as ≤ 31 ng/L or more than 31 ng/L and FSH was dichotomized as ≤ 11.5 mIU/mL or more than 11.5 mIU/mL based on results of the ROC analysis. Using these values, the specificity of the serum level of inhibin B for identifying azoospermic survivors was 45.0%, and the positive predictive value was 52.1%. The specificity for FSH was 74.1%, and the positive predictive value was 65.1%.

Conclusion: Neither serum inhibin B nor FSH is a suitable surrogate for determination of sperm concentration in a semen sample. Young men and their physicians should be aware of the limitations of these measures for assessment of fertility potential.

J Clin Oncol 31:1324-1328.

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Specificity of Problem-Solving Skills Training in Mothers of Children Newly Diagnosed With Cancer: Results of a Multisite Randomized Clinical Trial

Olle Jane Z. Sahler, Michael J. Dolgin, Sean Phipps, et al

pp 1329-1335

Purpose: Diagnosis of cancer in a child can be extremely stressful for parents. Bright IDEAS, a problem-solving skills training (PSST) intervention, has been shown to decrease negative affectivity (anxiety, depression, post-traumatic stress symptoms) in mothers of newly diagnosed patients. This study was designed to determine the specificity of PSST by examining its direct and indirect (eg, social support) effects compared with a nondirective support (NDS) intervention.

Patients and Methods: This randomized clinical trial included 309 English- or Spanish-speaking mothers of children diagnosed 2 to 16 weeks before recruitment. Participants completed assessments prerandomization (T1), immediately postintervention (T2), and at 3-month follow-up (T3). Both PSST and NDS consisted of eight weekly 1-hour individual sessions. Outcomes included measures of problem-solving skill and negative affectivity.

Results: There were no significant between-group differences at baseline (T1). Except for level of problem-solving skill, which was directly taught in the PSST arm, outcome measures improved equally in both groups immediately postintervention (T2). However, at the 3-month follow-up (T3), mothers in the PSST group continued to show significant improvements in mood, anxiety, and post-traumatic stress; mothers in the NDS group showed no further significant gains.

Conclusion: PSST is an effective and specific intervention whose beneficial effects continue to grow after the intervention ends. In contrast, NDS is an effective intervention while it is being administered, but its benefits plateau when active support is removed. Therefore, teaching coping skills at diagnosis has the potential to facilitate family resilience over the entire course of treatment.

J Clin Oncol 31:1329-1335.

Implementation of Universal Microsatellite Instability and Immunohistochemistry Screening for Diagnosing Lynch Syndrome in a Large Academic Medical Center

Brandie Heald, Thomas Plesec, Xiuli Liu, et al

pp 1336-1340

Purpose: In 2009, the Evaluation of Genomic Applications in Practice and Prevention recommended that all colorectal cancers (CRCs) be screened for Lynch syndrome (LS) through microsatellite instability (MSI) or immunohistochemistry (IHC). No studies report how this process is implemented on a health system–wide basis.

Methods: Since 2004, Cleveland Clinic has screened CRC specimens with MSI/IHC. Between January 2004 and July 2007, MSI/IHC results went only to the colorectal surgeon (approach 1). Between August 2007 and June 2008, colorectal surgeons and a genetic counselor received the MSI/IHC results, and the counselor e-mailed the colorectal surgeon regarding appropriate patients for genetic counseling (GC) referral (approach 2). After July 2008, the colorectal surgeon and counselor received MSI/IHC results, but the counselor contacted the patient to facilitate referral (approach 3). In approaches 2 and 3, patients were presumed to have sporadic CRC if the tumor lacked MLH1 expression and was also *BRAF* mutated or if the patient was diagnosed at age greater than 72 years and had no cancer family history.

Results: Abnormal MSI/IHC results occurred in 178 (16%) of 1,108 patients. In approach 1, 21 (55%) of 38 patients with abnormal MSI/IHC were referred for GC, 12 (32%) of 38 underwent GC, and 10 (26%) of 38 underwent genetic testing (GT). In approach 2, nine (82%) of 11 patients were referred for GC, seven (64%) of 11 underwent GC, and five (45%) of 11 underwent GT. In approach 3, 56 (100%) of 56 patients were referred for GC, 40 (71%) of 56 underwent GC, and 37 (66%) of 56 underwent GT. Time from referral to GC was 10-fold quicker in approach 3 than approach 1.

Conclusion: Implementation of universal MSI/IHC with GC/GT, along with effective multidisciplinary communication and plans of responsibility for patient contact, resulted in increased identification of patients with LS.

J Clin Oncol 31:1336-1340.

Fluorouracil, Leucovorin, and Irinotecan Plus Either Sunitinib or Placebo in Metastatic Colorectal Cancer: A Randomized, Phase III Trial

Alfredo Carrato, Anna Swieboda-Sadlej, Marzanna Staszewska-Skurczynska, et al

pp 1341-1347

Purpose: This double-blind, phase III study aimed to demonstrate that sunitinib plus FOLFIRI (fluorouracil, leucovorin, and irinotecan) was superior to placebo plus FOLFIRI in previously untreated metastatic colorectal cancer (mCRC).

Patients and Methods: Patients were randomly assigned to receive FOLFIRI and either sunitinib (37.5 mg per day) or placebo (4 weeks on treatment, followed by 2 weeks off [schedule 4/2]) until disease progression. The primary end point was progression-free survival (PFS). Secondary end points included overall survival, safety, and patient-reported outcomes. The correlation between genotype and clinical outcomes was also analyzed.

Results: In all, 768 patients were randomly assigned to sunitinib plus FOLFIRI (n = 386) or placebo plus FOLFIRI (n = 382). Following a second prespecified interim analysis, the study was stopped because of potential futility of sunitinib plus FOLFIRI. Final results are reported. The PFS hazard ratio was 1.095 (95% CI, 0.892 to 1.344; one-sided stratified log-rank $P = .807$), indicating a lack of superiority for sunitinib plus FOLFIRI. Median PFS for the sunitinib arm was 7.8 months (95% CI, 7.1 to 8.4 months) versus 8.4 months (95% CI, 7.6 to 9.2 months) for the placebo arm. Sunitinib plus FOLFIRI was associated with more grade ≥ 3 adverse events and laboratory abnormalities than placebo (especially diarrhea, stomatitis/oral syndromes, fatigue, hand-foot syndrome, neutropenia, thrombocytopenia, anemia, and febrile neutropenia). More deaths as a result of toxicity (12 *v* four) and significantly more dose delays, dose reductions, and treatment discontinuations occurred in the sunitinib arm.

Conclusion: Sunitinib 37.5 mg per day (schedule 4/2) plus FOLFIRI is not superior to FOLFIRI alone and has a poorer safety profile. This combination regimen is not recommended for previously untreated mCRC.

J Clin Oncol 31:1341-1347.

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Histomolecular Phenotypes and Outcome in Adenocarcinoma of the Ampulla of Vater

David K. Chang, Nigel B. Jamieson, Amber L. Johns, et al

pp 1348-1356

Purpose: Individuals with adenocarcinoma of the ampulla of Vater demonstrate a broad range of outcomes, presumably because these cancers may arise from any one of the three epithelia that converge at that location. This variability poses challenges for clinical decision making and the development of novel therapeutic strategies.

Patients and Methods: We assessed the potential clinical utility of histomolecular phenotypes defined using a combination of histopathology and protein expression (CDX2 and MUC1) in 208 patients from three independent cohorts who underwent surgical resection for adenocarcinoma of the ampulla of Vater.

Results: Histologic subtype and CDX2 and MUC1 expression were significant prognostic variables. Patients with a histomolecular pancreaticobiliary phenotype (CDX2 negative, MUC1 positive) segregated into a poor prognostic group in the training (hazard ratio [HR], 3.34; 95% CI, 1.69 to 6.62; $P < .001$) and both validation cohorts (HR, 5.65; 95% CI, 2.77 to 11.5; $P < .001$ and HR, 2.78; 95% CI, 1.25 to 7.17; $P = .0119$) compared with histomolecular nonpancreaticobiliary carcinomas. Further stratification by lymph node (LN) status defined three clinically relevant subgroups: one, patients with histomolecular nonpancreaticobiliary (intestinal) carcinoma without LN metastases who had an excellent prognosis; two, those with histomolecular pancreaticobiliary carcinoma with LN metastases who had a poor outcome; and three, the remainder of patients (nonpancreaticobiliary, LN positive or pancreaticobiliary, LN negative) who had an intermediate outcome.

Conclusion: Histopathologic and molecular criteria combine to define clinically relevant histomolecular phenotypes of adenocarcinoma of the ampulla of Vater and potentially represent distinct diseases with significant implications for current therapeutic strategies, the ability to interpret past clinical trials, and future trial design.

J Clin Oncol 31:1348-1356.

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Central Venous Catheter Care for the Patient With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Charles A. Schiffer, Pamela B. Mangu, James C. Wade, et al
pp 1357-1370

Purpose: To develop an evidence-based guideline on central venous catheter (CVC) care for patients with cancer that addresses catheter type, insertion site, and placement as well as prophylaxis and management of both catheter-related infection and thrombosis.
Methods: A systematic search of MEDLINE and the Cochrane Library (1980 to July 2012) identified relevant articles published in English.
Results: The overall quality of the randomized controlled trial evidence was rated as good. There is consistency among meta-analyses and guidelines compiled by other groups as well.
Recommendations: There is insufficient evidence to recommend one CVC type or insertion site; femoral catheterization should be avoided. CVC should be placed by well-trained providers, and the use of a CVC clinical care bundle is recommended. The use of antimicrobial/antiseptic-impregnated and/or heparin-impregnated CVCs is recommended to decrease the risk of catheter-related infections for short-term CVCs, particularly in high-risk groups; more research is needed. The prophylactic use of systemic antibiotics is not recommended before insertion. Data are not sufficient to recommend for or against routine use of antibiotic flush/lock therapy; more research is needed. Before starting antibiotic therapy, cultures should be obtained. Some life-threatening infections require immediate catheter removal, but most can be treated with antimicrobial therapy while the CVC remains in place. Routine flushing with saline is recommended. Prophylactic use of warfarin or low-molecular weight heparin is not recommended, although a tissue plasminogen activator (t-PA) is recommended to restore patency to occluded catheters. CVC removal is recommended when the catheter is no longer needed or if there is a radiologically confirmed thrombosis that worsens despite anticoagulation therapy.
J Clin Oncol 31:1357-1370.

FORTHCOMING REPORTS

Risk of Colorectal Cancer After Diagnosis of Endometrial Cancer: A Population-Based Study

Harminder Singh, Zoann Nugent, Alain Demers, et al

miR-155 in Acute Myeloid Leukemia: Not miR-ly a Prognostic Marker?

Cailin E. Joyce and Carl D. Novina

Benefits and Adverse Events in Younger Versus Older Patients Receiving Adjuvant Chemotherapy for Osteosarcoma: Findings From a Meta-Analysis

Marnie Collins, Miriam Wilhelm, Rachel Conyers, et al

Reduced Neuroanatomical Volumes in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

Bernward Zeller, Christian Tamnes, Adriani Kanellopoulos, et al

LUX-Lung 4: A Phase II Trial of Afatinib in Patients With Advanced Non–Small-Cell Lung Cancer Who Experienced Progression on Prior Treatment with Erlotinib, Gefitinib, or Both

Nobuyuki Katakami, Shinji Atagi, Koichi Goto, et al

A Critical Evaluation of Oncology Clinical Practice Guidelines

Bradley N. Reames, Robert W. Krell, Sarah N. Ponto, et al

Reduction of Cancer-Related Fatigue With Dexamethasone: A Double-Blind, Randomized, Placebo-Controlled Trial

Sriram Yennurajalingam, Susan E. Frisbee-Hume, J. Lynn Palmer, et al

Results of an International Randomized Phase III Trial of the mTOR Inhibitor, Ridaforolimus, Versus Placebo to Control Metastatic Sarcomas in Patients After Benefit From Prior Chemotherapy

George Demetri, Sant Chawla, Isabelle Ray-Coquard, et al

Eliminating Racial Disparities in Colorectal Cancer in the Real World: It Took a Village

Stephen S. Grubbs, Blase N. Polite, John Carney, et al

Randomized, Multicenter, Open-Label Study of Oxaliplatin Plus Fluorouracil/Leucovorin Versus Doxorubicin As Palliative Chemotherapy in Patients With Advanced Hepatocellular Carcinoma From Asia

Shukui Qin, Yuxian Bai, Ho Yeong Lim, et al

Evaluation of Tumor-Size Response Metrics to Predict Survival and Progression Free Survival in Western and Chinese Patients With First-Line Metastatic Colorectal Cancer

Laurent Claret, Manish Gupta, Kelong Han, et al

Pooled Analysis of the Prognostic and Predictive Effects of *KRAS* Mutation Status and *KRAS* Mutation Subtype in Non–Small-Cell Lung Cancer

Frances A. Shepherd, Caroline Domerg, Pierre Hainaut, et al

Correlation Between Financial Relationships With Commercial Interests and Research Merit and Prominence in Oncology Research

Beverly Moy, Angela R. Bradbury, Paul R. Helft, et al

Cediranib for Metastatic Alveolar Soft Part Sarcoma

Shivaani Kummar, Deborah Allen, Anne Monks, et al

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EDITORIAL

Clinical Trials of Cancer Cachexia Therapy, Now and Hereafter

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See accompanying article on page 1271

In the article accompanying this editorial, a clinical trial of melatonin for the treatment of cancer cachexia is reported by Del Fabbro et al.[1] Melatonin can be purchased over the counter or on the internet and thus is one of the many putative therapies for cancer cachexia that can be freely obtained by patients without consultation with a health care professional. The vast majority of such integrative therapies lack any evidence in support of their efficacy, other than anecdotal findings. The results of Del Fabbro et al are important because patients use these therapies at some expense and potentially some risk. The absence of either positive or negative findings at least means that patients are unlikely to experience any detriment from undertaking melatonin therapy, and at best these placebo-controlled and double-blinded findings would discourage their future use.

Cancer anorexia in particular is subject to substantial placebo effects, and it cannot be underestimated how important it is to conduct well-stratified, randomized, blinded, and controlled trials. The context of the Del Fabbro et al[1] study was within a program where there was excellent attention to pain and symptom management while patients were evaluated for eligibility and eventually included in the trial. This means that the standard of care for symptom management was not as much of a wild card as they might otherwise have been, especially as in multicenter studies with disparate standards of care.

The melatonin story is a good example of how optimistic results in open label and uncontrolled trials are deflated by the first controlled investigation. Preclinical studies may also inflate the hopes for a new cachexia therapy. On the surface of it, the evidence in animal models sounds quite compelling for pleiotropic beneficial actions of melatonin on appetite, intestinal transit, nutrient absorption, inflammation, and even antitumor effects. However, several of these findings were observed in healthy animals, in nonmalignant disease or a single cancer model. Indeed, there was no evidence as to whether melatonin has these effects in the presence of tumor and systemic inflammation, or whether it would be equally effective at early, intermediate, and late stages of cachexia.

During the time the study in the current report was developed and completed, there has been a thoughtful reconsideration of cancer cachexia by within the clinical cancer research community. This introspection has in part been motivated by the fact that there have been approximately 100 randomized clinical investigations of therapies for cancer cachexia and anorexia, yet many of them,[2-4] like the present one, have been negative and have not resulted in approved therapies. Research on the underlying biology of cancer cachexia has expanded dramatically,[5] especially in relation to its characteristic pronounced catabolism of skeletal muscle. Cachexia is now the subject of a series of biannual international conferences, a journal,[6] and a Society on Cachexia and Wasting Disorders. International consensus groups[7] have convened to address lack of consistency in defining cachexia, in the use of diagnostic criteria for cachexia and in the design of cachexia-related clinical trials. These consensus building efforts herald a paradigm shift in the design of clinical trials on cancer-associated cachexia.

Here are some of the new concepts that current and future cancer cachexia clinical trials are incorporating into their designs:

- Healthy adults are notably resistant to attempts to lose weight and the appearance of involuntary weight loss will always be regarded as the primary clinical sign of cachexia. With the understanding that cachexia is characterized by skeletal muscle loss with or without the loss of adipose tissue[7], the use of weight loss and weight gain of unspecified composition as study inclusion criteria and outcomes will fall aside, and be replaced by specific, sensitive, and precise measures of body composition such as dual energy x-ray and computed tomography. Bioelectrical impedance, noted to give results substantially discrepant from dual energy x-ray [8,9] in patients with cancer, is not a suitable alternative.
- It is also now appreciated that cancer cachexia represents a continuum with three clinically relevant phases—precachexia, cachexia, and refractory cachexia.[7] While many prior trials had included patients with advanced cachexia and near death,[1-4] current trials include cachexia therapy initiated at diagnosis and concurrently with antineoplastic therapy, a preventative approach starting intervention at the time of early onset. The term refractory delineates cachexia in patients who are entering the final stage of their cancer journey, at which time medical and ethical considerations change the focus of therapy. End of life is the time for cachexia interventions which have a rapid, if short-term, benefit such as corticosteroids or progestins as well as psychosocial suppport. It is of importance to understand that it can be the status of the cancer (metastatic, highly proliferative, and unresponsive to treatment), and the proximity to death, in addition to the severity of the cachexia, that may render a patient refractory. Consultation with end-of-life care teams will be valuable for the identification of the refractory patient.

- It is clear that cancer cachexia is a multifactorial syndrome characterized by reduced food intake and distinctive metabolic alterations involving skeletal muscle, adipose tissue, the central nervous and immune systems.[5,7] Based on expanded understanding of the fundamental biology, new cachexia therapy is increasingly based on distinct molecular targets, such as the skeletal muscle androgen receptor, myostatin, ghrelin, interleukin 6, and interleukin 1α. While there are numerous single agents currently under investigation, the potential for robust response to a single agent may be questioned. A defining feature of cachexia, as opposed to simple malnutrition, is that it cannot be fully reversed by nutritional support alone. Likewise, it is questionable as to whether an anabolic therapy can be effective in the absence of adequate supply of essential nutrients or in the presence of rampant inflammation and catabolic mediators. This has been taken as an argument for investigations of multimodal therapy such as graded resistance training/aerobic exercise, targeted nutrient supplementation, and pharmacologic intervention.
- Reduced food intake in cachexia has primary and secondary components.[7] The primary effects include decreased central drive to eat, chemosensory disturbances, and altered GI motility, which are centrally mediated constituents of sickness behavior. Secondary causes of impaired food intake are symptoms of cancer or cancer treatment such as stomatitis, diarrhea, constipation, dyspnea, and pain. These are often readily reversible with appropriate treatment. It will be difficult to test the efficacy of a treatment for cancer anorexia in the presence of poorly (or disparately) managed pain and symptoms, and thus a set of standards for symptom management will be adopted in a trial design.[1,7]
- Traditionally the primary end points of trials of cachexia therapy have been measures of body weight and food intake. More recently, regulatory agencies and cachexia experts have questioned the clinical benefit of the gain of a few kilograms of muscle or a few points on a visual analog scale of appetite. While clinical benefit cannot be defined by a single measure, ongoing trials in progress have adopted end points with a clearer definition of clinical benefit than in the past such as overall survival (ie, NCT01505530) and objective measures of power and speed on a stair-climbing test (ie, NCT00467844).

There is reason for optimism. The development of novel therapeutics, coupled with the utilization of state of the art methods and the standardization of design and end points in clinical trial design, promises a new phase of supportive oncology in which approved therapies will soon deliver improved quality of life, tolerance of antineoplastic therapy, and survival.[10]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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EDITORIAL

If at First You Don't Succeed: Stem-Cell Transplantation for Acute Myeloid Leukemia After First Relapse

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See accompanying article on page 1293

Therapy for younger patients with acute myeloid leukemia (AML) is administered with curative intent. After complete remission (CR) is achieved with initial induction therapy, some form of postremission therapy is required to prevent relapse, and the choice is generally between a few courses of high-dose cytarabine-based chemotherapy or one to two courses of chemotherapy followed by allogeneic stem-cell transplantation. The latter comes in a variety of different flavors, most often using fully human leukocyte antigen (HLA) –matched sibling donors, but now with an expanding choice of unrelated, cord blood, or haploidentical donors as well as a range of myeloablative or reduced-intensity pretransplantation conditioning regimens. Randomized trials have failed to show an advantage of autologous transplantation (perhaps because so many of the marrows were contaminated by minimal residual disease that was not detectable with the technology available at that time), and there is no benefit from continued maintenance chemotherapy.

It has been difficult to prove that allogeneic transplantation is superior to chemotherapy alone when applied to the broad, biologically heterogeneous population of younger patients with AML. The trials that have been performed are somewhat imperfect in that patients were assigned to transplantation if they had an HLA-matched sibling, rather than being strictly randomly assigned. In addition, many patients declined transplantation, leading to the imaginative so-called donor versus no donor comparisons that were intended to mimic intent-to-treat analyses.[1] A recent meta-analysis of these randomized trials has suggested that allogeneic transplantation in first CR provides the greatest advantage for patients in higher risk groups as defined by cytogenetics and somewhat less benefit for the markedly heterogeneous groups of patients who are characterized as intermediate risk.[2]

The relapse rate is lower after allogeneic transplantation because the graft versus leukemia effect makes an important contribution to the overall outcome. This is balanced by higher rates of treatment-related mortality and morbidity, although there have been improvements in transplantation techniques and considerably reduced short-term mortality in recent years.[3] And indeed, even as a card-carrying member of the nontransplanters union, I acknowledge and so inform my patients that the survival after transplantation has never been shown to be worse than with chemotherapy consolidation in the comparative trials.

When counseling patients in first remission, most clinicians also mention that the initial decision is only the first part of the calculation, given that patients who relapse can subsequently receive a transplant in second remission. That said, until now, this could only be stated in a general way because there have been virtually no systematic data that address the feasibility and outcome of later transplantation. Problems include the difficulties in achieving a second remission, the development of complications during reinduction that could preclude transplantation, the administrative delays imposed by insurers, delays in identifying unrelated donors if siblings are not available, and an appreciable post-transplantation relapse rate, among others.

Hence the importance of the large and unique analysis from the Medical Research Council (MRC) of the United Kingdom that accompanies this editorial.[4] This is a real-world experience in that the MRC enrolls an extraordinarily high fraction of United Kingdom patients with newly diagnosed AML onto clinical trials and has good follow-up of these individuals. The authors focus on 1,271 patients in first relapse, age 16 to 50 years, who had not received an allogeneic transplant in first CR; 19% of these relapsed patients were alive at 5 years after relapse with a major effect of cytogenetic risk category (32% for favorable, 17% for intermediate, and only 7% for high risk). Other salient findings included the following.

First, a perhaps higher than expected rate of second CR was achieved in 55% of patients, and the 5-year overall survival of these responders was 34%. The CR rate varied according to risk group and, although it is not stated explicitly, it is likely that the probability of second CR was strongly affected by the duration of first CR.[5,6]

Second, remarkably, 67% of the remitters could receive transplantations in second CR (perhaps because many of these patients had donors who were identified in first CR but chose not to undergo transplantation, and because they were being observed as part of a clinical trial) with a 5-year survival of 44% in those undergoing one of many different types of allogeneic transplantation. It remains to be seen whether such a high fraction of patients could receive transplantations in the United States, but emphasizes the importance of beginning donor searches at the time of diagnosis.

Third, chemotherapy alone could have served as salvage treatment for 16% of those achieving second CR who did not undergo

transplantation; most of these long-term survivors were in the subgroup with favorable cytogenetic or molecular findings (core binding factor leukemias and *NPM1*-mutated disease, respectively).

Finally, transplantation in first relapse without previous attempts at induction was disappointing and resulted in long-term disease-free survival of only 9%.

There remain a large number of unanswered questions and missing details. It is not known why some patients with HLA-matched siblings declined transplantation in first CR and whether these patients differ from those in first relapse. Nor is information provided about the reasons for treatment failure after transplantation in second CR. These patients were all enrolled onto clinical trials, and it is unclear whether results would be similar in the overwhelming majority of patients in the United States and elsewhere who do not have the guidance and discipline provided by clinical trials. Nonetheless, the MRC, to their everlasting credit, continues to overwhelm us with large numbers such that these results almost certainly provide reasonable estimates that others can use in clinical practice.

The authors estimated that similar results can be achieved for patients with favorable prognoses as well as for the large cohort of intermediate-risk patients, by reserving transplantation for those who relapse. This would require many fewer transplantations than if all were to undergo transplantation in first CR. Of course, it would be ideal to be able to tailor transplantation and treatment recommendations according to biologic features in individual patients. A large number of articles have been published in the last few years that describe multiple molecular abnormalities, present alone and in combination, that are not detectable by karyotyping; in particular, intermediate-risk AML includes probably dozens of molecularly definable subtypes.[6-8]

It seems likely that most if not all of the critical abnormalities will be identified in the near future, as more leukemias are genotyped, and that the discovery phase of the gene of the month club will soon be completed. And then, the hard work begins. After resolving the sometimes contradictory reports of the impact of specific patterns of genetic change on treatment outcome, it is hoped that these findings will provide insight into the pathogenesis of AML and permit truly targeted treatments à la imatinib mesylate for chronic myeloid leukemia. But as a humbling reminder, the first significant articles that described the prognostic impact of balanced chromosomal translocations, additions, and deletions on leukemia outcome were published about 30 years ago, and we still have minimal understanding of the biochemical mechanism(s) by which these changes promote leukemogenesis and influence response to cytotoxic treatment. Thus, the focus will need to shift from the perhaps more sexy discipline of molecular genetics to the difficult areas of medicinal biochemistry and drug discovery.

However, in the interim, we have to make recommendations to patients and in particular provide advice about transplantation in first CR to patients with molecular genetic findings that predict poorer outcome with chemotherapy. Most attention has focused on patients with mutations in the *FLT3* gene, which when altered by a mutation in the tyrosine kinase domain or by mutations producing internal tandem duplications (ITDs) in the transmembrane domain, provides a constitutive proliferative signal. Multiple retrospective analyses have suggested a higher relapse rate and lower survival in such patients, although there is controversy about whether there are differential effects of ITDs of different lengths or different allelic ratios of mutated to unmutated genes.[9]

It is tempting to recommend transplantation to all individuals with *FLT3* mutations, but the literature is contradictory in that one large donor/no donor analysis from the MRC did not show an advantage from allogeneic transplantation in such patients,[10] whereas another similar retrospective analysis from trials in Germany reached the opposite conclusion.[6] In addition, it is not automatic that resistance to chemotherapy can be overcome by transplantation. Indeed, a recent analysis by the European Group for Blood and Marrow Transplantation has shown a doubling of the relapse rate after transplantation in individuals with *FLT3* ITD mutations compared with patients with wild-type *FLT3*.[11] Similar patterns of higher relapse have been noted in patients who have undergone transplantation and who have other high-risk features,[12] including the so-called monosomal karyotype,[13] those in second or later remissions, and even those with just minimal residual disease before transplantation.[14]

In the short term, it would be helpful to our patients if data from the multiple, largely European studies that included an allogeneic transplantation option could be pooled to provide more quantitative data on the potential benefit of transplantation for *FLT3*-mutated and other discrete higher-risk AML groups. Until then, albeit with imperfect evidence, it is appropriate to offer transplantation in first CR to these higher-risk individuals, particularly given the very poor outcome should they relapse, as documented by the MRC.

Much of this discussion has centered on managing/preventing treatment failure. Indeed, most research has focused on mechanisms of leukemia cell drug resistance, with little attention on mechanisms that underlie sensitivity to treatment. Stated differently: why do we cure a substantial fraction of patients with AML using chemotherapy alone? One possibility is that chemotherapy actually killed the last clonogenic leukemia cell through cytotoxic mechanisms. I would think that this is likely to be uncommon. Another possibility might be that chemotherapy somehow induces re-expression of genes that were silenced during leukemogenesis by epigenetic or other means, permitting leukemia cell differentiation with elimination of the undifferentiated phenotype characteristic of AML.[15] Last, and perhaps most attractive because it may be amenable to therapeutic manipulation, it is possible that by unknown mechanisms, crude chemotherapy sometimes reverses immune tolerance, restoring immune surveillance and allowing suppression or elimination of the small amounts of residual disease that remain after successful cytoreduction.

Along the same lines, we have recently reported on a group of patients with acute leukemia and chronic myeloid leukemia who relapsed decades after their initial remission, including one patient with T-lineage acute lymphocytic leukemia who relapsed with the same karyotype as the original leukemia after more than 20 years of CR.[16] Within the last few years, I have also had two patients with acute progranulocytic leukemia who relapsed with acute promyelocytic leukemia after 8 and 13 years of CR, respectively. What produced the decades-long dormancy, and what went wrong after this long interval? One can only speculate, but one possibility is that immune surveillance again became insufficient, permitting leukemia regrowth or emergence of a subclone. In any event, it is interesting to think about the mechanisms that underlie success, with the possibility that further immune system evaluations could provide therapeutic clues in the future.

This article from the MRC[4] provides a wealth of longitudinal information that can be used in making transplantation recommendations for patients in first CR. It is an important example of what can

be accomplished with diligent long-term follow-up that addresses questions of clinical importance. It also reminds us that there is still considerable room for improvement using either modality and that leukemia cell drug resistance remains a formidable adversary. This is even truer for the large population of older patients with AML. It is my belief that further substantive progress will not come from cytotoxic therapy but rather from immunologic manipulations and the contributions of molecular biology, the latter in turn needing to have a more mechanistic focus.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ONCOLOGY GRAND ROUNDS

Acute Myeloid Leukemia in First Remission: To Choose Transplantation or Not?

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See accompanying article on page 1293

The Oncology Grand Rounds series is designed to place original reports published in the Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in* Journal of Clinical Oncology, *to patients seen in their own clinical practice.*

A 42-year-old woman presented with bruising and fatigue. Her WBC count was 10,370/μL, with a differential showing 5% polys, 5% monos, 10% lymphocytes, and 80% myeloid-appearing blasts, some of which contained Auer rods (Fig 1). Bone marrow examination revealed 90% infiltration with myeloid-appearing blasts, and flow cytometry analysis confirmed the diagnosis of acute myeloid leukemia (AML) with expression of CD33, CD13, and CD117. Cytogenetics revealed a normal female karyotype; molecular testing for *NPM1*, *FLT3*-ITD, and *CEBPα* mutations revealed wild-type status for each gene. The patient received induction therapy with daunorubicin 90 mg/m^2 per day for 3 days and continuous-infusion cytarabine 100 mg/m^2 per day for 7 days. After an induction course complicated by Gram-negative bacterial sepsis, her counts recovered by day 32, and bone marrow examination 6 weeks after diagnosis showed a complete remission. One week later she feels well and has normal physical and laboratory examinations. She is an only child (but has a common HLA type) and presents for discussion of postremission therapy options.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

This patient represents one of the most important clinical challenges in the management of adults with AML: whether to perform allogeneic stem-cell transplantation in first remission or employ a chemotherapy-based approach to further reduce the minimal residual disease burden after achievement of remission down to a level compatible with cure. This choice represents an emotional and psychosocial dilemma for most patients because the treatment modalities entail such different toxicities and promise for disease control. A chemotherapy-based approach (potentially including autologous stem-cell transplantation), although resource intense and associated with significant morbidity, carries a fairly low treatment-related mortality rate and (to a first approximation) no risk of long-term sequelae. On the other hand, for the average patient with AML, the risk of relapse during or after such an approach is well over 50%.[1] There is no question that the leukemia relapse rate is significantly lower if allogeneic stem-cell transplantation is chosen as the primary postremission therapy. The problem is that this modality, although becoming better tolerated in recent years, is associated with a significant rate of treatment-related mortality and appreciable rate of long-term issues such as graft-versus-host disease (GVHD), which can lead to a diminished quality of life. In short, many chemotherapy patients die as a result of relapsed leukemia, although salvage is possible, often by allogeneic transplantation in second remission, whereas patients who undergo allogeneic transplantation after first remission are more likely to die as a result of treatment-related complications.

The main question for the patient younger than age 60 years is: "What is the best chance of being alive, free of leukemia, several years from now?" Even this simple question involves the issues of quality of life, resource allocation, and patient preference. The answer is based on many nondefinitive and/or nonapplicable clinical trials conducted in the past, the results of which must be interpreted in the context of an improved understanding of the biology of leukemia as well as the management of transplantation complications. Second, inherent bias based on the type of practice carried out by the patient's physician may influence the decision. Biases may be based on experiential, personal, or other considerations. Physicians who participate in stem-cell transplantation seem more likely to recommend it, whereas those who do not may be more likely to recommend a chemotherapy-based approach.

Furthermore, the answer will not be the same for all patients with AML because this disease is heterogeneous. Although the treatment-related mortality associated with allogeneic stem-cell transplantation is roughly the same regardless of the biologic subtype of AML, the likelihood of cure with chemotherapy varies widely from 85% in acute promyeloctic leukemia (first-remission transplantation is never considered) to 65% in most patients with t(8;21) or inversion 16

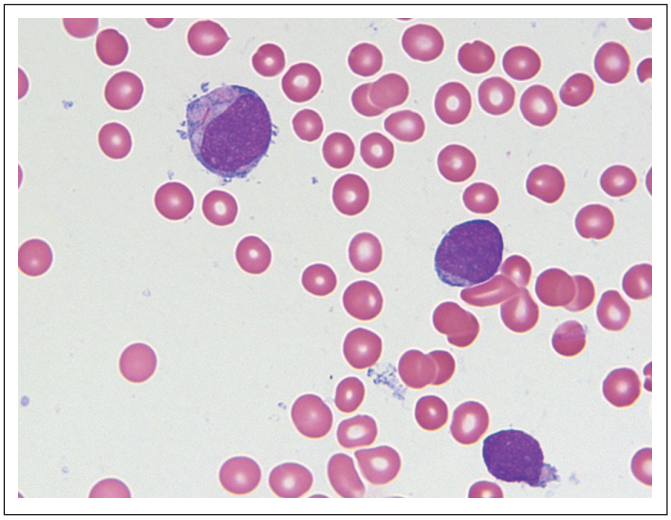

Fig 1. Peripheral blood smear (50× photomicrograph depicting monomorphic cells characterized by a high nuclear-to-cytoplasmic ratio, some with cytoplasmic Auer rods, consistent with acute myeloid leukemia).

(so-called core binding factor leukemias) down to well under 20% in those with complex cytogenetics.[2] Although the specifics of different cytogenetic classifications systems vary slightly, conventionally, patients with AML are grouped into three risk categories based on cytogenetics: favorable (inversion 16 or t(8;21)), adverse (> three abnormalities, monosomy 7, 5q−/5q, and others), and intermediate (all others; mostly normal cytogenetics).[2] Mutations in certain genes (particularly *NPM1* and *FLT3*) are being incorporated into the risk classification[3] (Table 1). It stands to reason that allogeneic transplantation is likely to be favored in those with a high risk of relapse and not as clearly indicated in those who have chemosensitive AML. Although

Table 1. Cytogenetic- and Genetic-Based Risk

Risk Group	Features	Approximate 4-Year Survival (%)	Approximate Prevalence (%)
Very high	Monosomal karyotype (two monsomies or one monosomy plus balanced translocation)	10	6
High	Complex (> three abormalities) or unfavorable (−7, 7q−, −5, 5q−, 3q , or t(6;9)) cytogenetics	20	12
Intermediate	Normal cytogenetics (with *FLT3* mutation or *FLT3*-ITD not present/*NPM1* wild type/*CEBPα* wild type) or other karyotype	35	25
	Inversion 16 or t(8;21) with *c-KIT* mutation	40	5
	Normal cytogenetics (with *FLT3*-ITD not present/*NPM1* mutation)	50	25
Favorable	Normal cytogenetics (with *CEBPα* biallelic mutation)	60	5
	t(8;21) or inversion 16 (with *c-KIT* wild type)	65	10
Very favorable	t(15;17)	85	12

logical, even such a conclusion is tentative given the fact that leukemia relapse is more common after stem-cell transplantation in patients with biologically unfavorable AML than in patients with more-tractable disease.[4] A vast majority of patients with AML have normal chromosomes and/or are considered to have intermediate prognosis. In this group, much attention has been paid to the influence of genetic abnormalities such as mutations in the *FLT3*, *NPM1*, *IDH1*/*IDH2*, *CEBPα*, and *DNAMT3* genes to further refine prognosis. The landscape in which mutations might confer prognostic or predictive data is changing rapidly[1]; moreover, it seems that stem-cell transplantation is becoming less toxic over time, especially given increased use of reduced intensity conditioning regimens.[4] As such, the evidence pertaining to whether patients in first remission should undergo transplantation is based on an evolving database.

The reality facing our patient in the case presentation is captured by the following questions: 1) Should I undertake more-toxic therapy (that I might or might not need), which will definitely affect my quality of life for 6 to 12 months, and possibly longer if I develop GVHD, to maximize the chance of curing my leukemia now? 2) Or should I undergo the relatively well-tolerated chemotherapy now and reserve transplantation (if needed and if possible) for after relapse? From a societal standpoint, one might want to favor a strategy in which the fewest transplantations are performed commensurate with a good outcome in the entire population of patients with AML. A clinical trial that would directly answer this question would be designed as follows: All patients with AML in first complete remission (CR1) who have an acceptable donor (which currently would probably include either a matched sibling or an unrelated 7 of 8 or 8 of 8 match) would be randomly assigned to either a chemotherapy-based approach (possibly allowing autologous stem-cell transplantation) versus allogeneic stem-cell transplantation from their best donor. No such trials have ever been conducted successfully because of the reluctance of many physicians to pass up the opportunity to use a donor if one exists.

If patients in CR1 choose to be treated with chemotherapy alone, they must accept the fact that they might not be salvageable when they relapse and that risk of relapse after transplantation in second remission is higher than the risk of relapse after transplantation in first remission. The Medical Research Council (MRC) database analyzed in the accompanying report by Burnett et al[5] is advantageous in that a large number of patients are observed from time of AML diagnosis until death; one can therefore assess the consequences of delaying transplantation until relapse, particularly with regard to the likelihood of reaching and benefitting from a second remission. The main findings are that relapse after allogeneic transplantation in first remission is associated with a dismal likelihood (7%) of long-term survival, whereas there is a better possibility of salvage should a patient relapse after being treated solely with chemotherapy (19% long-term survival). Of note, the data pertain to those between the ages of 16 to 49 years, largely come from an older era (unrelated allografts fared less well than would be expected today: 5-year survival, 39% *v* 58% for sibling allograft), and include autograft (5-year survival if performed in CR1, 47%) in the transplanted group. In the context of the available literature, do these data change the prevailing wisdom?

SUMMARY OF THE RELEVANT LITERATURE

In the trials that came closest to answering the question of whether to perform allogeneic transplantation in first remission, patients with

Table 2. Selected Prospective Trials Assigning Those With Sibling Donors to Allogeneic Transplantation

Study	No. of Patients	Age Range (years)	Overall Survival (%)* Allogeneic Transplantation (sibling donor)	Random Assignment ICC	Random Assignment Autologous Transplantation
GOELAMS[6]	367	15-50	53†	54	50
US Intergroup[7]	346	16-55	46‡	52	43
EORTC[8]	576	10-45	59	46	56

NOTE. Only statistically significant difference was superiority of ICC compared with autologous ($P = .05$) or allogeneic transplantation ($P = .04$) in US Intergroup trial.

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; ICC, intensive consolidation chemotherapy; GOELAMS, Groupe Ouest-Est d'étude des Leucémies Aiguës et autres Maladies du Sang.

*Four-year survival is given in first and second rows; 5-year survival is given in third row.

†Sibling-matched transplantation assignment only in patients age < 40 years.

‡Assigned to transplantation if sibling match or single antigen mismatch.

sibling donors were allocated to stem-cell transplantation, whereas those with no sibling donors were randomly assigned to standard chemotherapy or autologous transplantation (Table 1), in an era before it was concluded that unrelated donors were equivalent to sibling matches. A donor versus no-donor analysis was conducted. Those who had donors were considered to be in the allogeneic transplantation group, and those without donors were in the chemotherapy group. The rate of those with a donor actually undergoing transplantation is approximately 65%, although this varies widely among studies; treatment-related mortality from CR1 transplantation is also variable, but a rate of 15% to 20% is a reasonable approximation. The donor versus no-donor analysis tends to bias against allogeneic transplantation, but because of the competing risk of relapse or death before transplantation, this is the only fair way to analyze the data (eg, transplantation centers that report results from the time of transplantation will always look better). As summarized in Table 2, the EORTC (European Organisation for Research and Treatment of Cancer) trial[8] revealed a disease-free survival benefit with allogeneic or autologous transplantation compared with the chemotherapy-based approach. However, there was no overall survival benefit. The US Intergroup trial[7] showed a disease-free survival benefit for allogeneic transplantation but no overall survival benefit (overall survival favored chemotherapy). Finally, the GOELAMS (Groupe Ouest-Est d'étude des Leucémies Aiguës et autres Maladies du Sang) trial[6] demonstrated no disease-free or overall survival benefit for any transplantation approach.

Are these trials relevant in the modern era? Both chemotherapy and allogeneic stem-cell transplantation results have improved through the uniform use of truly myelointensive chemotherapy[9] plus improved management of infections and better anti-GVHD prophylaxis and treatment.[4] A contemporary donor versus no-donor analysis would be difficult because the population of those who have a donor has greatly expanded given recent good results with unrelated matched transplantation and cord blood donation. Third, the risk groups for AML have been refined. One of the original studies was retrospectively reanalyzed according to cytogenetic risk group, with the notion developing that CR1 transplantation was appropriate for those at poor risk and not for those at good risk, whereas the situation for those at intermediate risk was unclear.[2]

In a study in which molecularly defined risk was analyzed, the German Acute Leukemia Study Group[10] performed a donor versus no-donor analysis and found that allogeneic transplantation led to superior disease-free survival compared with chemotherapy in most subgroups of genetically defined patients with normal chromosomes except for those with *NPM1* mutations who did not have *FLT3* mutations. Still, there was no overall survival benefit in any group, probably because of salvage after relapse. This study probably contributed to the prevailing view that supports transplantation in most intermediate-risk patients. Recent data have potentially narrowed the group of favorable *NPM1*-mutant/*FLT3*–wild-type normal cytogenetic patients to those who also have an *IDH1* or *IDH2* mutation.[1]

Another key contribution has come from meta-analyses of all studies comparing allogeneic transplantation with chemotherapy. Although Yanada et al[11] and Cornellissen et al[12] evaluated five and three trials, respectively, Koreth et al[13] found approximately 16 studies that could be considered useful with regard to risk-adapted outcome for sibling allogeneic transplantation versus chemotherapy. The study concluded that there is a survival advantage with allogeneic transplantation for those with intermediate-risk and poor-risk cytogenetics, but the survival benefit in the intermediate-risk group only just reached statistical significance. The MRC report[5] argues against CR1 transplantation for intermediate-risk patients but supports the prevailing wisdom with regard to patients with CR1 AML with good or poor-risk cytogenetics. The MRC study shows that approximately 19% of all patients and 17% of intermediate-risk patients who do not undergo CR1 transplantation and relapse can expect to be long-term survivors. Given this salvage rate, Burnett et al[5] reach quantitative conclusions similar to those in the Koreth et al meta-analysis, but because the survival difference favoring CR1 allogeneic transplantation is so close, the MRC study makes a resource-use argument that allogeneic transplantation should be used only in CR2 for intermediate-risk patients.

SUGGESTED APPROACH TO MANAGEMENT

The management of adults younger than age 60 years with AML in first remission after induction chemotherapy is a continuously evolving issue; my current approach is shown in Figure 2. Until the 1980s, when transplantation was associated with high treatment-related mortality, and available chemotherapy was not very effective, the controversy raged. However, in the 1990s, when dose-intensive chemotherapy, largely based on the use of high-dose ara-C, led to a 40% disease-free and overall survival rate,[9] it seemed that transplantation could be avoided in most patients, because that was equal to the rate seen with transplantation. However, in the last decade, treatment-related mortality from transplantation declined, the heterogeneity of AML in terms of response to intensive chemotherapy was recognized, and allogeneic stem-cell transplantation, at least if a sibling donor was available, was recommended for most patients in remission except for those with features suggestive of a low degree of chemotherapy resistance, including patients with diagnostic chromosomes showing inversion 16 or t(18;21) and, more recently, those with normal cytogenetics with *NPM1* mutations but without an *FLT3*-ITD mutation. Given the widely accepted notion that a matched unrelated donor is now as effective and as safe as a matched sibling donor,[4]

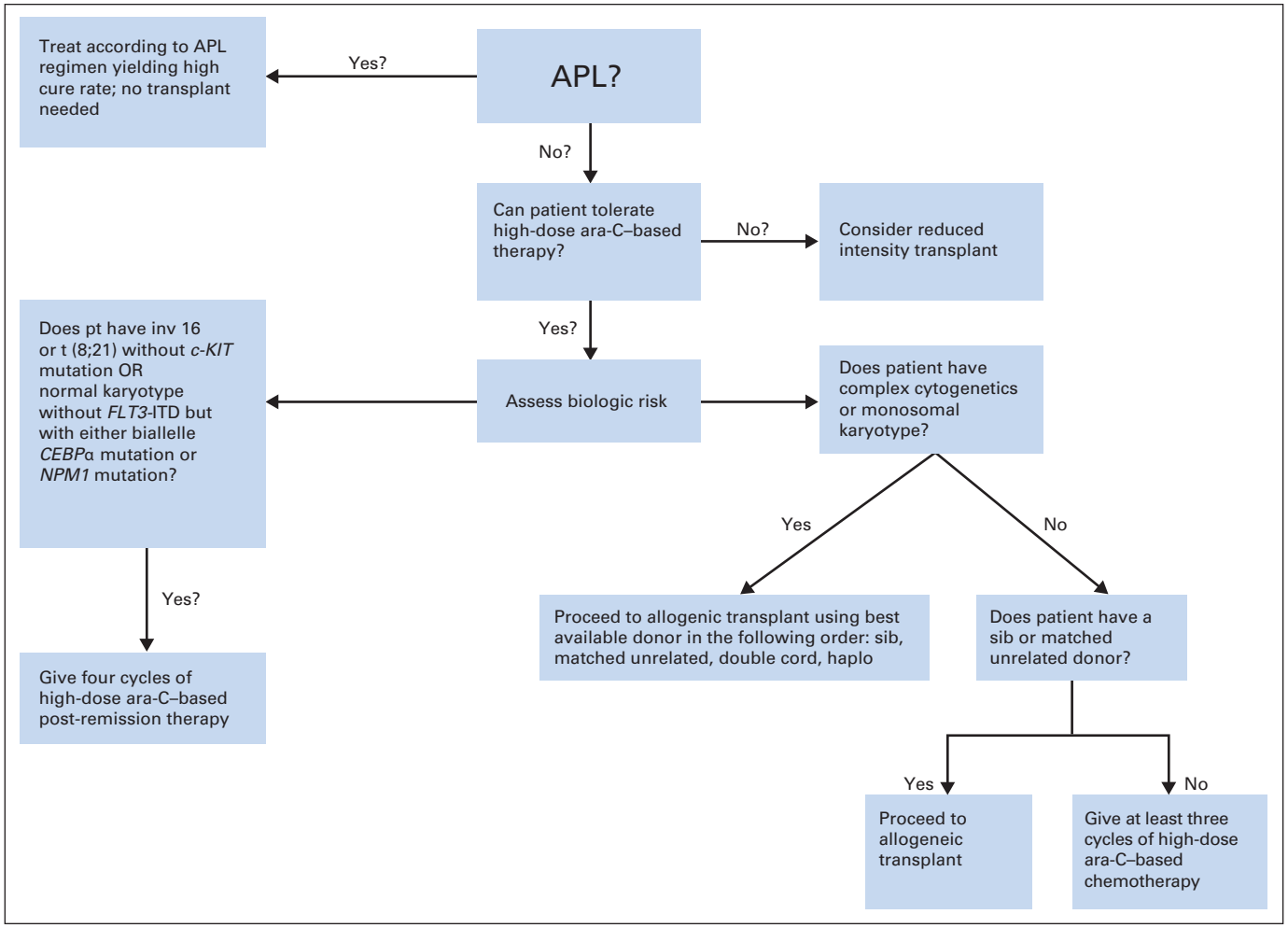

Fig 2. Algorithm for management of patients age 18 to 55 years with newly diagnosed acute myeloid leukemia in first complete remission. APL, acute promyeloctic leukemia; haplo, haplotype; sib, sibling.

allogeneic stem-cell transplantation for all but the best-risk patients who have a donor has been my recommended standard of care for younger adults.

The Burnett et al[5] study in *Journal of Clinical Oncology* provides important data about the realistic salvage rate (5-year survival, 19%) if patients defer CR1 transplantation. Autologous transplantation, never clearly shown to be superior to chemotherapy, can be substituted for dose-intensive chemotherapy but might make allogeneic transplantation in second remission more difficult. Moreover, double umbilical cord blood or haplotype-identical donor transplantation can be performed safely and offers an alternative for CR1 patients who lack a living matched donor.[4] The data in the Burnett et al report do not significantly alter the overall conclusion if one accepts the notion that allogeneic transplantation in CR1 in intermediate-risk patients is a controversial topic and requires a prolonged discussion with the patient regarding relative personal values and competing risks.

More-widespread use of genetic markers will change the landscape. For example, not all core binding factor cytogenetics patients are the same. The impact of *c-KIT* mutations in the presence of an inversion 16 or t(8;21) chromosomal abnormality is largely thought to confer adverse prognosis,[14] and perhaps on that basis alone, this would justify allogeneic stem-cell transplantation rather than the more commonly held view mandating high-dose ara-C–based therapy in what otherwise seems to be a favorable prognostic subgroup. Second, perhaps only those *NPM1*-mutant/*FLT3*-ITD–wild-type patients who also have an *IDH1* or *IDH2* mutation who have the best risk[1] should be referred for chemotherapy, whereas *NPM1*-mutant/*FLT3*-ITD–wild-type, *IDH1*/*IDH2*–wild-type patients should be referred to allogeneic stem-cell transplantation. However, it is worth re-emphasizing that poor prognosis does not necessarily mean that the outcome will be better with allogeneic stem-cell transplantation.

Data in the MRC report might help the 42-year-old patient in the case presentation make her own decision. She can now perhaps more precisely evaluate the option of delayed transplantation if she does not want to undertake the significant risks of allogeneic stem-cell transplantation performed now when she potentially could be cured with chemotherapy. Hopefully, further improvement in both transplantation and targeted therapy (ie, FLT3 inhibitors in patients whose blasts at diagnosis have an *FLT3* mutation) or use of epigenetic modification therapy (ie, histone deceatylase or DNA methyltransferase inhibitors) could make results with either option better.

In summary, although I recommend allogeneic stem-cell transplantation for the nonfavorable patient with AML in

remission, such as the patient depicted in our case, the alternative strategy of receiving high-dose ara-C–based chemotherapy in first remission followed by close observation and transplantation in second remission if obtained is a reasonable alternative. Moreover, I have assumed that a matched unrelated donor is equivalent to a matched sibling donor. The patient's decision should include an understanding that the upfront mortality savings might not be realized by successful transplantation in second remission if disease control cannot be achieved or if the patient relapses after CR2 transplantation. Improvements in antileukemic therapy and supportive care should make each of the alternatives more favorable but may not make the decision any easier. In the case of our patient, she chose to undergo matched unrelated-donor allogeneic transplantation, which was complicated by moderate acute GVHD. She is currently doing well, without evidence of leukemia relapse.

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COMMENTS AND CONTROVERSIES

Multiplex Genetic Testing for Cancer Susceptibility: Out on the High Wire Without a Net?

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The integration of germline genetic testing into cancer care has been a gradual process. It has taken years to construct the evidence base to define the optimal management of individuals who carry mutations in cancer susceptibility genes. Although this evidence remains imperfect, it would be less robust if it were not for the role of the American Society of Clinical Oncology and other organizations, which have firmly and consistently endorsed the principle that genetic susceptibility testing should, if at all possible, be offered in the context of clinical trials with appropriate informed consent and follow-up.[1-3] Substantial investment in research by individual centers and large international collaborations, including PROSE, the Hereditary Breast-Ovarian Cancer Study Group, and the Breast Cancer Family Registry, has generated data to guide clinical interventions, such as preventive salpingo-oophorectomy in *BRCA* mutation carriers.[4-6]

It is clear that the genetic architecture of cancer predisposition can be quite complex. Researchers have identified numerous cancer susceptibility syndromes and their causative genes.[7] The risk of cancer at a given site may be elevated by mutations in one of a number of different genes, and a mutation in a particular gene often increases risk for more than one type of cancer. There are high-penetrance genes that result in autosomal-dominant predispositions recognizable by pedigree analysis, and moderate-penetrance genes, in which mutations are associated with lower relative risks (usually 2 to 5) and in which mutations may not cosegregate with implicated cancers in individual families.

In the traditional model of clinical cancer genetics, patients are evaluated on the basis of family history or patient-specific factors such as age at diagnosis or disease histology. After appropriate evaluation and consent, testing is performed, usually serially, for the most likely genetic causes.[8] The advantage of this approach is that testing is more specific, because genes that are unlikely to be mutated are not analyzed. Importantly, the process of pretest counseling for each gene allows the patient to participate in the decision of whether to pursue a particular test after considering the clinical and personal utility of the result. However, the standard approach of serial testing is time consuming and expensive. In contrast, next-generation sequencing (NGS) technologies now allow simultaneous analysis of multiple susceptibility genes (multiplex testing) at a cost that is modestly greater than single-gene testing (currently $3,855 to $5,466 at one commercial laboratory).[9,10] Multiplex testing employs the same technologies as whole-exome and whole-genome sequencing but generates a more limited amount of information about predefined target genes.

Multiplex test panels that evaluate high- and moderate-penetrance genes are now available and are being marketed as a means of quickly assessing cancer susceptibility, either generically or for a specific disease site (Table 1). The multiplex approach has evident advantages, especially the potential for greater time and cost efficiency. It may be particularly useful in situations where: there is significant genetic heterogeneity; the prevalence of actionable mutations in one of several genes is significant; and it is difficult to predict which gene may be mutated on the basis of phenotype or family history. Examples of such situations include early-onset pheochromocytoma/paraganglioma and Lynch syndrome. However, there are nontechnical challenges that must be met to ensure the most responsible and effective implementation of these new technologies.

ENSURING APPROPRIATE PRETEST COUNSELING

When testing for highly penetrant cancer syndromes began, there were concerns that many patients would experience significant anxiety on learning that they carried a predisposing mutation. Fortunately, those concerns have not been borne out. Individuals receiving mutation-positive results do describe an increase in anxiety, but this seems to return to baseline with the passage of time in most cases.[11,12] For this reason, cancer predisposition testing is generally perceived to be safe, although there are some who experience prolonged, clinically significant anxiety after testing. However, the studies establishing safety included careful pretest counseling, which may affect generalizability of results. Individuals at highest risk for post-test distress may not pursue testing, because they fear significant anxiety in the event of a mutation-positive result. This process of defensive self-selection is likely enhanced by the receipt of adequate information regarding the implications of the test being performed, including information about the recommended medical interventions in the event of a positive result. Current counseling models are not designed to provide in-depth education for simultaneous testing of multiple genes for diverse syndromes linked by a single cancer, and unprepared individuals receiving unanticipated mutation-positive results in this setting could experience much more distress than has been reported to date. It will be important to rapidly develop new

Table 1. Genes Analyzed in Commercially Available Multiplex Panels

Gene	Ambry Genetics*				University of Washington Laboratory Medicine†	
	CancerNext	BreastNext	ColoNext	OvaNext	BROCA	ColoSeq
APC	●		●		●	●
ATM	●	●		●	●	
ATR					●	
BABAM1					●	
BAP1					●	
BARD1	●	●		●	●	
BMPR1A			●		●	
BRIP1	●	●		●	●	
CDH1	●	●	●	●	●	●
CDK4					●	
CDKN2A					●	
CHEK1					●	
CHEK2	●	●	●	●	●	
FAM175A/Abraxas					●	
MLH1	●		●	●	●	●
MRE11A	●	●		●	●	
MSH2-positive *EPCAM*	●		●	●	●	●
MSH6	●		●	●	●	●
MUTYH	●	●	●	●	●	●
NBN	●	●		●	●	
PALB2	●	●		●	●	
PMS2	●		●	●	●	●
PRSS1					●	
PTEN	●	●	●	●	●	●
RAD50	●	●		●	●	
RAD51					●	
RAD51B					●	
RAD51C	●	●		●	●	
RAD51D					●	
RBBP8					●	
RET					●	
SMAD4	●		●		●	
STK11	●	●	●	●	●	●
TP53	●	●	●	●	●	●
TP53BP1					●	
UIMC1					●	
VHL					●	
XRCC2					●	
XRCC3					●	

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†Seattle, WA.

counseling models to ensure that individuals undergoing multiplex testing are providing truly informed consent for that testing, the lack of which may have serious ramifications.

As examples of the new challenges of multiplex testing, the inclusion of *TP53* and *CDH1* (encoding E-cadherin) on panels without specific pretest counseling may be particularly problematic. Germline *TP53* mutations result in vastly elevated risks for a wide range of cancers, including childhood cancers. Surveillance recommendations for *TP53* mutation carriers, including children, are evolving but are of uncertain efficacy.[13] For this reason, a substantial proportion of individuals in families with known *P53* mutations decline testing when offered in the context of careful pretest counseling.[14] Likewise, individuals with deleterious mutations in *CDH1* have a $>$ 80% chance of developing diffuse gastric cancer, and prophylactic gastrectomy is strongly recommended.[15] *CDH1* mutations are also associated with increased risk of lobular breast cancer, and mutations are sometimes found in breast cancer families without a history of gastric cancer.[16] Without appropriate pretest counseling, the identification of *CDH1* mutations in breast cancer–only families could lead to significant anxiety because of the need to consider prophylactic gastrectomy in mutation carriers.

ENSURING APPROPRIATE CLINICAL INTERPRETATION OF MODERATE-PENETRANCE TESTING

As described earlier, a number of moderate-penetrance genes have been discovered; mutations of these genes confer relative risks of 2 to 5.

Some of these have been well studied by international consortia. Most have not. The appropriate clinical response to a moderate-penetrance mutation remains unclear, even for genes for which there is a fairly extensive evidence base, such as *CHEK2*.[17,18] The optimal management of carriers of moderate-penetrance mutations remains incompletely defined, and presymptomatic testing for moderate-penetrance genes does not provide the same clarity of guidance as testing for high-penetrance genes, even when a mutation is known to be present in a family. In particular, negative testing may not justify a relaxation of surveillance, and the magnitude of risk associated with a positive result may not warrant incremental surveillance (or preventive surgery) beyond that justified by family history alone. Data are not available to provide risk estimates for individuals who may have multiple moderate-penetrance mutations. In circumstances where pharmacologic risk-reducing agents are available, it is not clear that the presence or absence of moderate-penetrance mutations should determine eligibility for chemoprevention. Finally, there is a concern that patients who have not received adequate pretest counseling may be unable to differentiate the levels of risk associated with different genes in a multiplex panel. Such individuals may opt to seek highly sensitive, but less specific, surveillance strategies as well as prevention approaches intended for individuals carrying high-penetrance mutations (eg, preventive surgery).

ENSURING APPROPRIATE INTERPRETATION OF VARIANTS OF UNCERTAIN SIGNIFICANCE

Sequencing a gene (whether by Sanger or NGS techniques) will frequently identify variants that alter the predicted amino acid sequence of the resulting protein (missense mutation). For many cancer susceptibility genes, there are no assays to directly assess whether a particular amino acid change impairs the function of the resulting protein. There are a number of computational tools that attempt to predict whether a given amino change is likely to be functionally significant—for example, as a consequence of structural changes in an important part of the protein—or whether the altered amino acid is highly conserved through evolution (suggesting that it may be functionally important).[19-24] However, without a direct functional assay, algorithms to predict the clinical impact of a particular amino acid change have uncertain clinical validity and should not be used in isolation to guide patient management. Such alterations must be considered variants of uncertain clinical significance (VUCS). It is usually inappropriate to alter management guidelines on the basis of a VUCS result; rather, family history is used to guide enhanced screening or prevention decisions. Unfortunately, clinicians ordering genetic testing often misinterpret VUCS results and make recommendations to patients that should be reserved for individuals carrying clearly deleterious mutations.[25] Because the likelihood of detecting VUCS is directly related to the number of genes tested, multiplex genetic testing presents a significant risk of generating inappropriate recommendations that may result in harm to the patient. Appropriate pretest education of patients and providers is necessary to limit the harm that could result from misinterpretation of these types of test results. At the same time, improved computational and functional approaches to elucidate the clinical significance of these variants remain vital requirements. Testing laboratories, in particular, should be cognizant of the possible clinical consequences of the wording of their reports and should be transparent in describing their procedures for inference of the functional consequences of a particular sequence variation. Describing a variation as potentially or probably pathogenic could result in interventions such as preventive surgery, which would not be appropriate without robust evidence that the variation indeed resulted in an increase in cancer risk. Interpretations based on evolutionary conservation algorithms alone, for example, would not meet that standard.

DISCUSSION

Multiplex testing is the natural result of advances in our understanding of the genetic architecture of cancer predisposition and in sequencing technology. However, multiplex testing in parallel is qualitatively different from the current serial approach to genetic testing. Existing pretest counseling and informed consent models were not designed to address the challenges posed by multiplex testing; new educational and operational approaches must be developed. At a minimum, we would suggest that these new approaches achieve three major goals.

First, individuals considering multiplex testing should be helped to understand the specific implications (for themselves and their families) of clearly deleterious mutations in each of the high-penetrance genes being tested. Individuals should especially be made aware of the spectrum of cancers associated with mutations in each of these genes, particularly cancers that have not been seen in the family to date. As part of the pretest counseling process, individuals should be given the opportunity to opt out of learning certain results of gene sequencing that they do not wish to learn (eg, *TP53*).

Second, individuals should understand that even clearly deleterious mutations in different genes are associated with substantially different risks for cancer of a specific site. Individuals should understand that it is not yet clear how best to individualize the clinical recommendations based on different mutations in different genes, but one size does not fit all.

Third, individuals should explicitly understand the real chance that multiplex testing may identify VUCS and that such variants should not be treated as if they were deleterious and causative of a cancer predisposition without strong evidence that such is the case.

Pending the development of these new counseling approaches, we recommend that multiplex testing be performed in the context of carefully designed follow-up studies to limit the potential for harm and maximize benefit to patients. This was the approach adopted when high-penetrance cancer predisposition testing first became available; the reason *BRCA1/2* and Lynch testing provides clear information to patients and their families is the result of the investment in research, both nationally and internationally, that led to clinical care standards. Each of the genes on the available multiplex panels are uncommonly mutated; therefore, collaborative epidemiologic work will be critical because large numbers of patients will be needed to adequately assess risk and to inform clinical management.[26] The issues discussed in this article will be exponentially magnified with whole-exome and whole-genome sequencing. It is vital that we proceed thoughtfully so that we may ensure the safety of patients and their families as we work to realize the promise of NGS and multiplex testing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ORIGINAL REPORT

Effects of Melatonin on Appetite and Other Symptoms in Patients With Advanced Cancer and Cachexia: A Double-Blind Placebo-Controlled Trial

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See accompanying editorial on page 1257

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ABSTRACT

Purpose
Prior studies have suggested that melatonin, a frequently used integrative medicine, can attenuate weight loss, anorexia, and fatigue in patients with cancer. These studies were limited by a lack of blinding and absence of placebo controls. The primary purpose of this study was to compare melatonin with placebo for appetite improvement in patients with cancer cachexia.

Patients and Methods
We performed a randomized, double-blind, 28-day trial of melatonin 20 mg versus placebo in patients with advanced lung or GI cancer, appetite scores ≥ 4 on a 0 to 10 scale (10 = worst appetite), and history of weight loss ≥ 5%. Assessments included weight, symptoms by the Edmonton Symptom Assessment Scale, and quality of life by the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Differences between groups from baseline to day 28 were analyzed using one-sided, two-sample *t* tests or Wilcoxon two-sample tests. Interim analysis halfway through the trial had a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule. Decision boundaries were to accept the null hypothesis of futility if the test statistic $z < 0.39$ ($P \geq .348$) and reject the null hypothesis if $z > 2.54$ ($P \leq .0056$).

Results
After interim analysis of 48 patients, the study was closed for futility. There were no significant differences between groups for appetite ($P = .78$) or other symptoms, weight ($P = .17$), FAACT score ($P = .95$), toxicity, or survival from baseline to day 28.

Conclusion
In cachectic patients with advanced cancer, oral melatonin 20 mg at night did not improve appetite, weight, or quality of life compared with placebo.

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INTRODUCTION

Melatonin is a pleiotropic hormone that may modulate multiple mechanisms promoting cancer cachexia, including inflammation, autonomic failure, and malabsorption. Initially believed to be synthesized exclusively in the pineal gland and primarily involved as a circadian messenger of light and dark, melatonin is now recognized to have multiple actions[1] and is synthesized in diverse tissues.[2] Circulating melatonin is primarily derived from the pineal gland but is synthesized in even greater quantities locally by the GI system,[3] possibly in response to feeding.

Melatonin supplementation stimulates appetite in animals,[4] and its presence in the digestive tract is associated with intestinal transit and nutrient absorption.[5] Melatonin may also have antitumor activity through an antimitotic[6] effect and suppression of tumor linoleic acid uptake,[7] and in a preliminary trial, it improved the efficacy of arterial chemoembolization for hepatocellular carcinoma.[8]

Several studies have evaluated the effect of melatonin on symptoms such as poor appetite, fatigue, and depression in patients with cancer. Patients with metastatic solid tumors randomly assigned to supportive care plus melatonin for 3 months had better weight stabilization and lower levels of tumor necrosis factor α than patients receiving supportive care alone.[9]

A similar subsequent trial of melatonin for patients with untreatable solid tumors showed that cachexia, weakness, anorexia, and depression occurred more frequently in the group receiving supportive care alone.[10] In more recent trials, the same group of investigators reported decreased symptoms,

improved survival,[11] and fewer adverse effects in patients with solid tumors who were also given melatonin at night. No adverse effects were reported in any of these trials despite the use of a relatively high dose of 20 mg at night. Although patients were randomly assigned, it is important to note that none of the trials were double blind or placebo controlled. On the basis of these studies, it seemed that an inexpensive medication such as melatonin could improve symptoms and quality of life in patients with cancer, without causing adverse effects.

The primary objective of this study was to determine whether melatonin would improve appetite in patients with advanced cancer with cachexia, as defined by an improvement of 1.5 in appetite score from baseline on the Edmonton Symptom Assessment Scale (ESAS). Our secondary objective was to determine whether melatonin would increase weight and lean body mass and improve symptoms and quality of life as measured by the ESAS, Functional Assessment for Chronic Illness Therapy–Fatigue (FACIT-F), and Functional Assessment of Anorexia/Cachexia Therapy (FAACT) scores, respectively.

PATIENTS AND METHODS

Design

This study was a single-center, double-blind, parallel-group trial of adult patients with advanced lung or GI cancer equally randomly assigned (1:1) to 28 days of melatonin 20 mg at night versus placebo. All patients were given the option of receiving melatonin after 28 days.

Patients were enrolled from the supportive care clinic and solid tumor clinics at The University of Texas MD Anderson Cancer Center (MDACC). During the trial, the study was expanded to a second site, the Joan Karnell Cancer Center at University of Pennsylvania. This second site was terminated after enrolling two patients because continued support for a research coordinator was not possible.

Intervention

Melatonin (Medisca, Plattsburgh, NY) and matching placebo were compounded into capsules by the investigational pharmacy at MDACC. Investigational pharmacists dispensed either melatonin or placebo capsules according to a computer-generated random assignment list. The RANLST program, software prepared in the Department of Biostatistics at MDACC and supported by a National Cancer Institute grant, was used. Treatment allocation was concealed from patients, investigators, and study coordinators enrolling the participants. All patients were counseled and given dietary advice by a dietician at baseline.

Patients

Advanced cancer was defined as metastatic or locally recurrent disease, and patients were stratified according to those actively receiving treatment for their cancer versus those who were not. Inclusion criteria were age $\geq$ 18 years, appetite score $\geq$ 4 on a 0 to 10 scale (10 = worst appetite), and a history of weight loss $\geq$ 5% within 6 months. Premenopausal women with childbearing potential who had a positive pregnancy test were excluded. Patients unable to maintain oral intake or with dementia, delirium, or a Karnofsky performance score less than 40 were excluded. Patients who had uncontrolled symptoms that could impact appetite or caloric intake such as nausea, pain, or depression were excluded until their symptoms had stabilized for at least 2 weeks. Patients with untreated vitamin B_{12} deficiency or endocrine abnormalities that could affect appetite, such as thyroid dysfunction (thyroid-stimulating hormone $\leq$ 0.50 or $\geq$ 10 mIU/L) and hypoadrenalism, were excluded. Patients on melatonin supplements or medications with potential appetite-stimulating activity, such as megestrol acetate, corticosteroids, or thalidomide, were excluded unless they had been on a stable dose for more than 2 weeks and continued to experience poor appetite.

Assessments

Demographic data included performance status, tumor type, sex, age, and percentage weight loss.

ESAS. The ESAS[12] assesses the following 10 symptoms experienced by patients with cancer during the previous 24 hours: pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, sleep disturbance, and feelings of well-being. The severity of each symptom is rated on a numerical scale of 0 to 10 (0 = no symptom, 10 = worst possible severity). The ESAS is both valid and reliable in the assessment of the intensity of symptoms in patients with cancer.

FACIT-F. The FACIT-F[13] is a well-validated quality-of-life instrument widely used for the assessment of cancer-related fatigue in clinical trials. It consists of 27 general quality-of-life questions divided into four domains (physical, social, emotional, and functional), plus a 13-item fatigue subscore. The patient rates the intensity of fatigue and its related symptoms on a scale of 0 to 4. The total score ranges between 0 and 52, with higher scores denoting less fatigue.

FAACT subscale. The 12-item FAACT subscale questionnaire[14] has been validated in patients with advanced cancer.

Body composition and weight. Body composition and weight were measured using bioimpedance analysis (BIA). BIA is a noninvasive method of estimating body composition based on the ability of lean tissue to conduct an electrical current better than fat. The Tanita TBF-310 (Tanita, Tokyo, Japan) body composition analyzer/scale was used to measure total weight, total body fat, and total body lean mass.

Toxicity. A toxicity questionnaire was done at baseline and then at 14-day intervals until day 56.

Statistical Analysis

The trial was approved by the MDACC Institutional Review Board. Informed consent was obtained from each participant before study enrollment.

Patients were randomly assigned to receive melatonin or placebo in a 1:1 ratio, with the change in appetite between baseline and 4 weeks being the primary end point. The two groups were stratified at the time of random assignment by whether or not the patient was receiving systemic chemotherapy. Appetite was measured with a 0- to 10-point scale using the ESAS. Previous studies by the senior author using appetite stimulators[15,16] have shown significant increases in the range of one half a standard deviation, or approximately a 1.5-point change on a 0 to 10 scale. We also believe that this difference is of clinical importance.

To declare the above difference to be statistically significant, assuming a one-sided significance level of .05 and 80% power, we needed 50 evaluable patients per group. We believed that this medium effect size corresponded to the minimal clinically relevant difference. We used a one-sided test for the primary end point because of previous knowledge of differences expected to be found. All other tests were two-sided. No corrections were made for multiple tests. A *t* test was used to evaluate the difference between groups.

Intent-to-treat analysis was conducted using repeated measures analysis of variance including the time point of 4 weeks, with baseline included as a covariate. These analyses included the main effects of group and time and a group-time interaction. Other variables analyzed and compared by group included weight gain and changes in percent lean muscle mass, the FAACT, the FACIT-F, and other variables from the ESAS.

The interim analysis of efficacy and toxicity was scheduled when half of the patients had been evaluated (25 patients per group). To provide for an overall one-sided significance level of approximately $P = .05$ for the study, the interim analysis had a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule (EaSt, version 5; Cytel Software Corporation, Cambridge, MA). The decision boundaries for the interim test were to accept the null hypothesis of no treatment difference (futility) if the test statistic z was less than 0.39 ($P \geq .348$) and to reject the null hypothesis if z was greater than 2.54 ($P \leq .0056$). Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

For each group, the numbers of patients who were randomly assigned, received intended treatment, and were analyzed for the primary outcome are shown in Figure 1. The diagram includes information on the

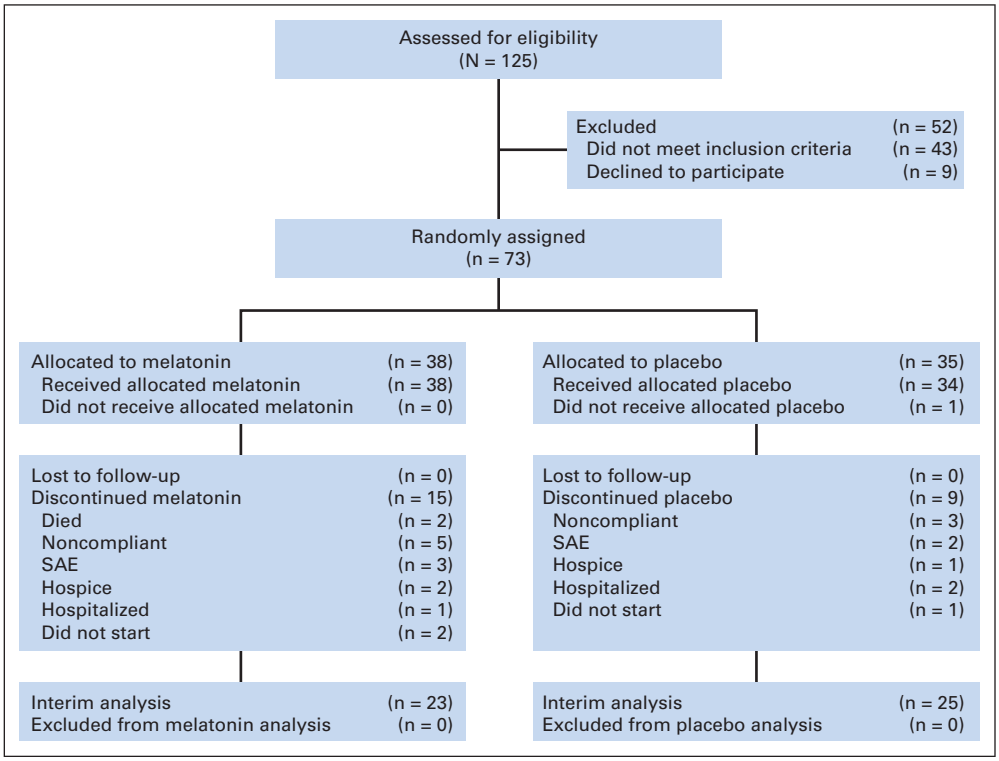

Fig 1. CONSORT diagram. SAE, severe adverse event.

excluded patients. Age-eligible patients were recruited from July 2006 to October 2010. Of the 73 randomly assigned patients with baseline scores, 48 patients had both baseline and week 4 measurements. Baseline characteristics of the two groups are listed in Table 1. No significant differences between groups were found in changes from baseline to week 4 in the appetite score using a one-sided two-sample *t* test ($P = .80$). There were also no differences between melatonin and placebo groups after 4 weeks regarding weight, body composition including fat-free mass, symptom scores, and quality-of-life outcomes as measured by FACIT-F and FAACT (Table 2). There was no difference in survival between the two groups (Fig 2), although all patients were given the option of continuing on melatonin after 4 weeks of enrollment. There were no treatment-related deaths, and the number of patients experiencing adverse events by maximum grade was similar in the melatonin (n = 37) and placebo groups (n = 34). We found no significant differences between patients receiving systemic chemotherapy and those on no systemic chemotherapy. The statistical collaborator presented the results to the MDACC Data Monitoring Committee at the yearly Data and Safety Monitoring Board (DSMB) review, while the primary investigator and other collaborators remained blinded. At the fourth yearly DSMB review, when 48 of 50 patients were evaluated for the primary end point, the DSMB requested a modification to the interim test to be made because the number of patients was close to the formal interim stopping rule. The stated early stopping rule was slightly modified to have its first review when 48 patients had been evaluated. The boundary for early stopping was crossed, and the DSMB recommended early stopping because of a low probability of finding significant results for the primary end point if the study were to continue.

This planned interim analysis, when half of the patients were enrolled, had stopping rules in place a priori that allowed for the early termination of the study in light of evidence that patients in the two groups had similar improvement (early stopping as a result of futility). Although there were no significant findings for group differences in appetite, when melatonin and placebo patients were analyzed as a group, significant correlations were found between percent weight change (from baseline to day 28) and appetite ($P = .024$) and depression ($P = .03$). The change in C-reactive protein (CRP) levels from baseline to day 28 showed no difference ($P = .98$) between the melatonin and placebo arms. Subgroup analysis was performed on 15 patients receiving melatonin who had CRP levels obtained at baseline and at day 28. Wilcoxon two-sample tests did not find significant differences in appetite ($P = .75$), fatigue ($P = .18$), or other ESAS scores when comparing patients with a decline in CRP versus those with the same or an increase in CRP.

DISCUSSION

Melatonin was not effective for improving appetite or other symptoms and did not improve quality of life in patients with advanced GI or lung cancer. Our study was stopped for futility after interim analysis of the data, which suggested that the results were not likely to change even with a larger sample size. Our dose of 20 mg of melatonin is unlikely to be the cause of the negative result. This dose is much higher than the 0.5- to 5-mg dose typically used for other conditions such as jet lag,[17] and there was no difference in the frequency of adverse effects between melatonin and placebo. Other

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Placebo Arm (n = 35) No. of Patients	%	Melatonin Arm (n = 38) No. of Patients	%
Age, years				
Mean	59		62	
Range	36-76		32-86	
Female	15	43	12	32
Race				
White	26	74	21	56
Black	6	17	13	34
Hispanic	2	6	3	8
Asian	1	3	0	
Cancer				
Digestive	22	63	19	50
Respiratory	13	37	19	50
Performance score				
70-90	27	77	27	71
50-60	8	23	11	29
Weight, kg				
Median	66		67	
Interquartile range	55-76		56-79	
Extent of weight loss, %				
Median	10		11	
Interquartile range	7-15		8-16	
Fat-free mass, kg				
Median	51		51	
Interquartile range	43-62		44-60	
ESAS scores				
Pain				
Median	2		3	
Interquartile range	0-4		2-5	
Fatigue				
Median	5		5	
Interquartile range	2-7		3-7	
Nausea				
Median	0		1	
Interquartile range	0-3		0-3	
Depression				
Median	0		2	
Interquartile range	0-5		0-5	
Anxiety				
Median	0		2	
Interquartile range	0-3		0-5	
Drowsiness				
Median	3		3	
Interquartile range	0-5		0-5	
Shortness of breath				
Median	0		2	
Interquartile range	0-5		0-6	
Appetite				
Median	6		7	
Interquartile range	4-9		6-8	
Sleep				
Median	3		5	
Interquartile range	1-7		3-7	
Well-being				
Median	5		5	
Interquartile range	2-7		3-7	

Abbreviation: ESAS, Edmonton Symptom Assessment Scale.

Table 2. Quality-of-Life Questionnaires and Symptom Scale Outcomes

Outcome	Change in Score (day 28 − baseline) Melatonin (n = 23)	Placebo (n = 26)	*P*
FAACT cachexia subscale			.95
Median	0	−0.5	
Interquartile range	−3 to −2	−2 to −1	
FACIT-F			.65
Median	−1	3.2	
Interquartile range	−13 to −12	−7 to −12	
Weight*			.17
Median	−0.8	−1.0	
Interquartile range	−2.3 to 0.15	−2.6 to 2	
Appetite*			.80
Mean	−0.83	−1.19	
SD	2.6	2.3	
95% CI	−1.9 to 0.2	−2.1 to −0.3	
Depression*			.28
Median	0	0	
Interquartile range	−1 to 0	−1 to 0	
Pain*			.30
Mean	0.09	0.38	
SD	2.0	2.0	
95% CI	−0.73 to 0.91	−0.39 to 1.15	
Well-being*			.72
Median	−0.39	−0.96	
Interquartile range	−1.9 to 1.1	−2.2 to 0.3	
Insomnia*			.62
Median	−1	−0.5	
Interquartile range	−3 to −1	−2 to −1	

Abbreviations: FAACT, Functional Assessment of Anorexia/Cachexia Therapy; FACIT-F, Functional Assessment for Chronic Illness Therapy–Fatigue; SD, standard deviation.
*According to a 0 to 10 score by the Edmonton Symptom Assessment Scale where 10 equals worst score.

trials showing improved clinical outcomes also used doses of 20 mg, but unfortunately, interpretation of their results is severely limited by methodologic issues such as a lack of blinding and absence of placebo controls.[9,10] The 4-week duration of treatment is also of sufficient length to obtain benefit from an effective intervention for appetite. Past studies of thalidomide and megestrol acetate have shown a rapid improvement of symptoms within 10 days and 2 weeks, respectively. There was no difference in survival between the two groups, and although patients receiving placebo were allowed to receive melatonin after the primary end point had been measured, the median survival of patients was only 134 days on placebo and 140 days on melatonin. Despite the option to change treatment and the possibility of a wash out of any positive effects on survival, analysis of survival was reasonable because patients were on study for more than 20% of the time until death.

There may be other reasons why no difference was found between melatonin and placebo regarding appetite and other clinical outcomes. Both melatonin and placebo groups in our study received symptom control and palliative care in an outpatient clinic throughout the duration of the study, and there was a significant association between weight gain (or less weight loss) and improved appetite and depression. There was no difference, however, in the change from baseline to day 28 between the two arms.

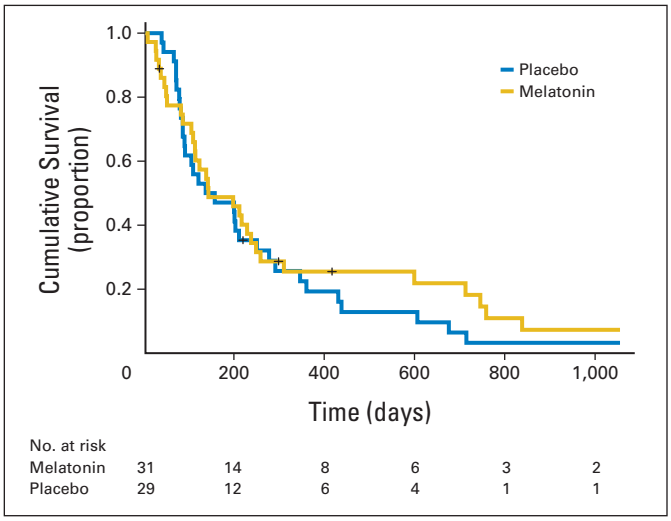

Fig 2. Survival between melatonin (gold; median survival, 140 days; 95% CI, 37 to 243 days) and placebo (blue; median survival, 134 days; 95% CI, 4 to 264 days; $P = .43$) arms.

It is possible that the measured benefit from a specific therapeutic intervention such as melatonin may be not be as marked when accompanied by optimal symptom management in the placebo arm. Although melatonin is reported to modulate tumor necrosis factor α levels and other cytokines[19,20] in patients with solid tumors, melatonin had no effect on CRP levels in our study. Elevated CRP levels have been associated with poor prognosis in patients with cancer, and CRP is regarded as a surrogate marker for the proinflammatory cytokine interleukin-6.

This apparent lack of an anti-inflammatory effect is compatible with the findings of another study in patients with advanced GI cancer, in whom melatonin had no effect on tumor necrosis factorα and other proinflammatory cytokines.[21] The overall inconsistent effect of melatonin on the proinflammatory response associated with cachexia is difficult to explain but may be a result of heterogeneity of tumor type and stage between studies. Although some patients in both groups responded with improvement in symptoms, it is possible that others may have been refractory[22] to the intervention because of their advanced disease. However, all patients enrolled onto our study were ambulatory and had similar characteristics as those admitted to previous studies of melatonin reporting positive outcomes. These unblinded studies found melatonin to be an effective intervention for cachexia, fatigue, and depression in patients with advanced cancer with untreatable metastatic solid tumors.[9,10]

Other intervention studies using ghrelin[23] and megestrol acetate[15,16] have also shown improved appetite and symptom burden in patient populations with advanced cancer where specific tumor therapy was no longer effective or indicated. A consensus classification of cancer cachexia has attempted to define patients who may be at the early precachexia phase and those who may be at the other end of the cachexia trajectory who are refractory to any interventions targeting weight or lean body mass. The concept of refractory cachexia, as defined by this expert panel, has no empirical confirmation, although a recent trial of fish oil for patients with GI cancer showing objective improvements in lean body mass provides some preliminary support for this model of cachexia staging. Patients were referred at initial diagnosis,[24] suggesting the benefit was likely a result of the early inception point, because two large randomized controlled trials and several prior systematic reviews had concluded that fish oil was of no benefit in patients with advanced cancer.

Melatonin might also be a more effective therapy if used much earlier in the disease trajectory, and this should be a consideration in the design of any future intervention trials for appetite or cachexia. However, it should be noted that based on current criteria, which includes a WHO performance status of 3 to 4 and survival less than 3 months, our trial participants would not be considered as having refractory cachexia. Our patients had better performance status, with a Karnofsky score between 70 and 90 in more than 70% of trial participants, and a longer median survival.

The strengths of our study include the double-blind, placebo-controlled design. Although 32% of our patients did not complete the study, this is consistent with other symptom intervention trial[25,26] in the palliative care population with advanced disease. Despite restricting our study population to patients with either advanced lung or GI cancer, there is likely to be some heterogeneity regarding prognosis and functional status because of different tumor types, concurrent chemotherapies, and disease trajectories. Other limitations include the absence of objective functional outcomes and more accurate measures of lean body mass such as dual-energy x-ray absorptiometry (DEXA) or computed tomography (CT) scan. Although there are no guidelines for selecting the most appropriate modalities to measure body composition, DEXA measurements and single-slice CT scans taken in the third lumber vertebra are more precise and reproducible but are more expensive and invasive than BIA.[27] We did not use these modalities because our patients were no longer undergoing routine CT scans and the potential benefit of using DEXA measurements was outweighed by the additional costs and the patient burden of further tests. Although the accuracy of BIA is poor compared with CT scan and DEXA, BIA does demonstrate good short-term precision (test-retest reliability) in patients with advanced cancer,[28] with a precision error of 1%, and may therefore be useful in measuring changes of body composition over time.[29]

In cachectic patients with advanced lung or GI cancer, oral melatonin 20 mg at night did not improve appetite, weight, or quality of life compared with placebo. More research is required to determine whether melatonin has a role in the supportive care of patients earlier in their disease trajectory.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Egidio Del Fabbro, Lynn Palmer, Eduardo Bruera
Collection and assembly of data: Egidio Del Fabbro, Rony Dev, David Hui
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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ORIGINAL REPORT

Sex Differences in the Return-to-Work Process of Cancer Survivors 2 Years After Diagnosis: Results From a Large French Population-Based Sample

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To investigate the effects of clinical, sociodemographic, and occupational factors on time to return to work (RTW) during the 2 years after cancer diagnosis and to analyze whether sex differences exist.

Patients and Methods
This study was based on a French national cross-sectional survey involving 4,270 cancer survivors. Time to RTW was estimated through the duration of sick leave of 801 cancer survivors younger than 58 years who were employed during the 2-year survey. Multivariate analysis of the RTW after sick leave was performed using a Weibull accelerated failure time model.

Results
We found some sex differences in the RTW process. Older men returned to work more slowly than older women ($P = .013$), whereas married men returned to work much faster than married women ($P = .019$). Duration dependence was also sex-specific. In men, the time spent on sick leave was independent of the probability of returning to work, whereas in women, this duration dependence was positive ($P < .001$). For both men and women, clinical factors including chemotherapy, adverse effects, and cancer severity were found to delay RTW ($P = .035$, $P = .001$, and $P < .001$, respectively). Survivors investing most strongly in their personal lives also delayed their RTW ($P = .006$), as did those with a permanent work contract ($P = .042$). The factor found to accelerate RTW was a higher educational level ($P = .014$).

Conclusion
The RTW process 2 years after cancer diagnosis differed between men and women. A better knowledge of this process should help the national implementation of more cost-effective strategies for managing the RTW of cancer survivors.

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INTRODUCTION

Recent progress in the early diagnosis of cancer has increased the number of working-age adults with cancer, and improvements in cancer treatment have led to an increased likelihood of long-term disease-free survival. Cancer can therefore now be considered as a transient health shock that is no longer likely to prevent survivors from returning to their workplace.[1]

From a societal perspective, long periods of sick leave have a heavy economic impact on society at large because of the indirect costs owing to the loss of productivity.[2] From the patients' perspective, long periods away from work are also likely to cause a loss of income and financial difficulties.[3,4] In addition, because return to work (RTW) helps patients to regain a normal life, it can be expected to enhance their social well-being, self-esteem, and quality of life.[5,6]

The literature on the RTW of cancer survivors is quite recent. Various authors have reported that most people return to work a few months after cancer diagnosis[6,7] and have documented the effects of disease-related and work-related factors, as well as patients' sociodemographic characteristics on their ability to RTW.[8-15] However, less attention has been paid to the factors contributing to the duration of cancer patients' sick leave. In France, absence from work because of cancer is covered by the National Health System, which provides workers with daily allowances that largely offset their loss of income during the sick-leave period (for up to 3 years). Workers on sick leave are regarded as being employed. Thus the time to RTW within the 2-year survey can be studied through the analysis of the

duration of the sick leave period. Cox proportional hazards model has been commonly used in cancer studies to analyze time to RTW, assuming the independence between the time elapsing during sick leave and the probability of returning to work. Studies in the field of labor economics have suggested, however, that some duration dependence often occurs, and this should be taken into account when analyzing the RTW process.[16,17] Studies on this topic have also stressed the need to distinguish between men and women because they behave differently in terms of the labor supply, which may in turn affect other labor market outcomes differently.[18] The factors underlying the RTW process certainly have a different impact, depending on whether the individual involved is a man or woman.[19]

This study therefore focused on the role of clinical, sociodemographic, and occupational characteristics of cancer survivors in the RTW process. Sex differences were addressed taking into account the duration dependence issue. The study was based on data obtained on a representative French national sample of 4,270 cancer survivors interviewed 2 years after cancer diagnosis.

PATIENTS AND METHODS

Study Population

A French national cross-sectional survey was launched in 2004 to investigate the living conditions of adult patients with cancer 2 years after cancer diagnosis.[20,21] It included 13,923 people diagnosed with cancer, who were randomly selected from the Long Duration Disease File of the National Health Insurance Fund between September and October 2002. This is a representative sample of cancer survivors alive in 2004 by one of the three main Health Insurance Schemes covering approximately 96% of the French population. Eligibility was restricted to adult patients diagnosed with first cancer. All eligible patients were invited to send back their signed informed consent. The study was approved by the French National committee on Informatics and Freedom. Among the 6,957 eligible patients with cancer, 4,460 agreed to participate (response rate, 64.1%). The final study sample consisted of 4,270 persons (Fig 1).

Data Collection

People were asked by telephone about their occupational situation during the 2-year study period (occupational status at the time of diagnosis, current work situation, duration of the last sick leave because of cancer) and their working conditions (type of job, work contract, work schedules, and income). Medical information about the disease (cancer type, disease stage at diagnosis, type of treatments, and evolution of the disease 2 years after diagnosis) was also collected. A three-category adverse effects variable was computed using the responses to two questions about the adverse effects people experienced: no adverse effects/slightly disturbing adverse effects and very disturbing adverse effects. A continuous variable (from 0 to 1) giving each patient's cancer prognosis was calculated based on the cancer survival rate 5 years after first diagnosis weighted by both the stage of the disease and the age at the time of diagnosis. In addition, they were asked to answer a three-category question about their priorities in life since diagnosis: "I attach more importance to my personal life"; "I attach equal importance to my personal and working life"; and "I attach more importance to my working life."

Outcome

The main outcome was the time to RTW after sick leave, defined as the number of months elapsing between the first day of sick leave due to cancer and the first day on which the patient actually returned to work.

Patients

The analysis was based on a sample of 1,150 participants who declared that they were employed during the 2 years covered by the survey (at diagnosis in 2002 and 2 years later) and were younger than 60 years (the French legal retirement age) at the time of the interview. Because no data were available on 144 patients' episodes of sick leave, these patients were dropped from the analysis. Our final study sample therefore included 1,006 patients meeting all the eligibility criteria (Fig 1).

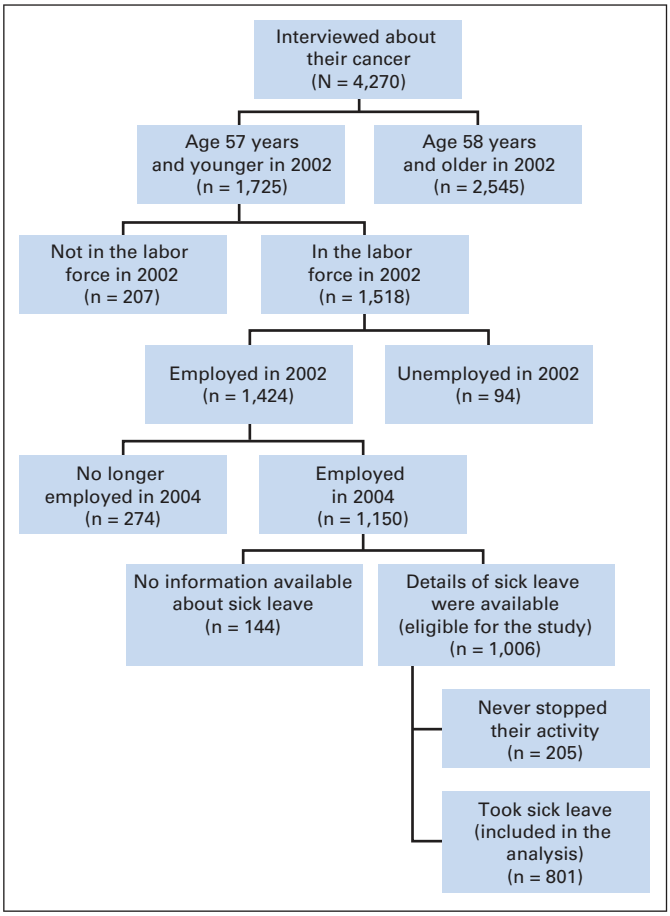

Fig 1. CONSORT diagram of the sample included in the survey.

Statistical Analysis

χ^2 tests and *t* tests were used to compare individual characteristics and duration of sick leave between men and women. Kaplan-Meier curves were drawn up showing the RTW process during the 2-year period, depending on sex.

Multivariate analysis was performed by implementing a Weibull accelerated failure time (AFT) model[22] allowing duration dependence to be considered (ie, to verify whether the probability of end of sick leave at any point in time depends on the amount of time that has already elapsed). AFT models provided accelerating factors (AF), which were interpreted in a similar way to hazard ratios: AF less than 1 (AF $>$ 1) indicated a longer (shorter) time to RTW.

A pooled model with a dummy variable distinguishing between men and women was estimated (model 1). Although this model allows verifying sex differences, it did not provide additional information about the observed characteristics at the origin of these differences. For this reason, a second pooled model was estimated with the set of observed characteristics interacted with the sex dummy variable (model 2).

It is important to notice that models 1 and 2 impose the strong assumption that duration dependence is the same for men and women. To relax this assumption, a third estimation (model 3) was carried out stratifying by sex. The global likelihood-ratio (LR) test was computed to test the pertinence of the stratified estimation of separate Weibull parameters. All the statistical analyses were computed with the R software.[23] For a detailed description of the econometric method, see Appendix (online only).

Table 1. Demographics and Clinical Characteristics of the Patients in the Sample

Characteristic	Women (n = 544)		Men (n = 257)		Together (n = 801)		No Sick Leave (N = 205)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Women	544	100			544	67.9	110	53.7*
Men			257	100	257	32.1	95	46.3*
Average age, years								
Mean	47.9		49.3		48.4		48.5	
SD	7.3		8.3		7.6		8	
Living with a partner								
Yes	418	76.8	216	84.0†	634	79.1	167	81.5
No	126	23.2	41	16.0†	167	20.9	38	18.5
Educational level								
No high school qualifications	97	17.8	51	19.8	148	18.5	39	19.0
Junior high school	189	34.7	106	41.2†	295	36.8	76	37.1
High school certificate	102	18.8	39	15.2	141	17.6	35	17.1
> High school level	156	28.7	61	23.8	217	27.1	55	26.8
Occupational group at diagnosis								
Farmers, manual workers	56	10.3	97	37.7*	153	19.1	46	22.4
Shopkeepers, crafts workers	17	3.1	24	9.4*	41	5.2	23	11.2*
Higher level professionals and managers	64	11.8	46	17.9†	110	13.7	32	15.6
Lower level professionals	137	25.2	53	20.6	190	23.7	51	24.9
Clerical and similar workers	270	49.6	37	14.4*	307	38.3	53	259*
Work contract at cancer diagnosis								
Permanent	460	84.6	215	83.7	675	84.3	149	72.7*
Fixed-term	47	8.6	14	5.4	61	7.6	17	8.3
Self-employed	37	6.8	28	10.9	65	8.1	36	17.6*
Missing values							3	1.4
Average monthly income per person in the household at diagnosis in Euros								
Mean		1,672.6		1,598.3		1,648.7		1,739.3
SD		1,167.8		1,064.2		1,135.3		2,311.4
Tumor type								
Colon/rectum	26	4.8	35	13.6*	61	7.6	15	7.3
Breast	358	65.8	0		358	44.7	61	29.8*
Prostate	0		32	12.5	32	4	15	7.3‡
Upper aerodigestive tract-lung	16	2.9	61	23.7*	77	9.6	15	7.3
Other urogenital tumors	60	11	28	10.9	88	11	32	15.6‡
Malignant hemopathy	27	5	40	15.6*	67	8.4	16	7.8
Other cancer	57	10.5	61	23.7*	118	14.7	51	24.9*
Average prognosis index§								
Mean	64.2		42.8		57.3		63,4	
SD	18.8		21.5*		22.1		18.2*	
Treatment								
Surgery only	89	16.3	82	31.8*	169	21.1	89	43.4*
Surgery and chemotherapy	57	10.5	37	14.5	95	11.8	19	9.3
Surgery and radiotherapy	122	22.5	35	13.7*	157	19.6	40	19.3
Surgery, chemotherapy, and radiotherapy	242	44.5	49	18.9*	293	36.6	39	19.2*
Other combination (including watchful waiting)	34	6.2	54	21.2*	87	10.8	18	8.8
Disease status								
Progressive disease	45	8.3	25	9.7	70	8.7	6	2.9*
Nonprogressive disease	499	91.7	232	90.3	731	91.3	199	97.1*
Side effects								
None or only slightly disturbing	214	39.4	96	37.4	311	38.8	129	62.9*
Yes, rather disturbing	218	40	89	34.6	307	38.3	45	22.0*
Yes, very disturbing	112	20.6	72	28.0†	183	22.9	31	15.1

(continued on following page)

Table 1. Demographics and Clinical Characteristics of the Patients in the Sample (continued)

Characteristic	Women (n = 544) No.	Women (n = 544) %	Men (n = 257) No.	Men (n = 257) %	Together (n = 801) No.	Together (n = 801) %	No Sick Leave (N = 205) No.	No Sick Leave (N = 205) %
Life priorities since diagnosis								
Attach more importance to their personal lives	372	68.4	165	64.3	538	67.2	104	50.7*
Attach equal importance to their personal lives and their work	149	27.4	80	31	227	28.4	88	42.9*
Attach more importance to their work	23	4.2	12	4.7	36	4.5	13	6.4
Average duration of sick leave, months								
Mean	10.5		8.1		9.8			
SD	6.9		6.9		7.0			
Censored‖	147	27	92	35.8	239	29.8		

NOTE. Symbols in the "Men" column denote comparisons between women and men; symbols in the "No Sick Leave" column denote comparisons between the patients included in the sample and those removed.
Abbreviation: SD, standard deviation.
*Significant differences at a 1% CI.
†Significant differences at a 5% CI.
‡Significant differences at a 10% CI.
§The prognosis index ranged between 0 and 100 (the worst and best prognosis, respectively).
‖Censored data correspond to individuals still on sick leave at the time of the interview (ie, it was not possible to know the complete duration of the period of sick leave).

RESULTS

Sample Description

Of the 1,006 eligible patients, 205 (20.3%) practically never stopped working during the observation period and were therefore excluded from the analysis (Table 1). They tended to be men, shopkeepers or artisans, self-employed, and have a better prognosis. They tended less frequently to have progressive disease, adverse effects, and a stronger investment in their personal life. The characteristics of the remaining 801 patients included in our analysis are also summarized in Table 1. Men were more likely to be living maritally, to have higher educational levels, and to be farmers or manual workers. They also experienced very disturbing adverse effects more frequently. The cancer type and treatment obviously differed between men and women: more men underwent only surgery, whereas more women underwent sequential treatment involving surgery, chemotherapy, and radiotherapy (the routine treatment for breast cancer).

RTW Rates by Sex

The Kaplan-Meier survival curves giving the probability of RTW after sick leave over time, depending on sex, are shown in Figure 2. The median duration of sick leave was the same with both sex (12 months, not significant). However, the shape of the curves differed, and they crossed 12 months after diagnosis. Six months after diagnosis, 36% of the men and 25% of the women had returned to work ($P = .006$). At 24 months, 65% and 72% of the men and women, respectively, had returned to work ($P = .042$).

Multivariate Analysis of Duration of Sick Leave With Sex Interaction Terms

Table 2 presents the factors significantly associated with time to RTW after sick leave, along with the corresponding AFs and CIs. Model 1 (first column of Table 2) showed the existence of a statistically significant difference between men and women ($P = .03$) in the RTW rate. This difference indicates that men were 29.2% (AF = 1.292) more likely to return to work than women at each point in time.

In model 2 (with sex interaction term), some clinical factors were found to be significantly associated with the RTW process, independently from sex. Chemotherapy (alone or combined with other types of treatment) decelerated RTW (AF = 0.746, $P = .035$), as well as disturbing reported adverse effects (AF = 0.703, $P = .001$ for rather

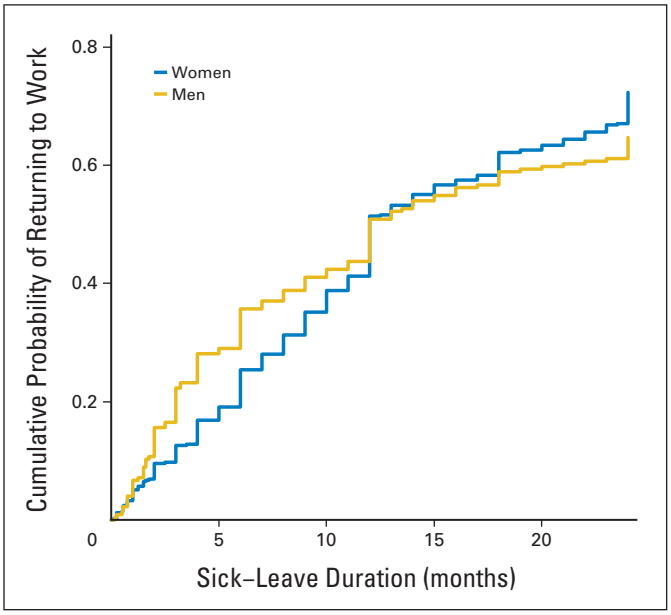

Fig 2. Kaplan-Meier estimation of the duration of sick leave, depending on sex.

Table 2. Pooled Weibull Regression for Men and Women of Main Factors Predicting Return to Work After Sick Leave: Sex-Crossed Effects

Variable	Model 1: Pooled Model, All (n = 801)		Model 2: Pooled Model With Sex Interactions, All (n = 801)			
					Interactions (men = 1)	
	AF*	95% CI	AF*	95% CI	AF*	95% CI
Sex						
Male	1.292†	1.014 to 1.645	0.962	0.037 to 2.714		
Female	1		1			
Age	0.984‡	0.973 to 0.995	0.992	0.979 to 1.005	0.970†	0.947 to 0.993
Living with a partner						
Yes	1.222†	1.006 to 1.486	1.123	0.906 to 1.393	1.866†	1.107 to 3.146
No	1		1			
Educational level						
No formal education	1		1			
Junior high school	1.190	0.933 to 1.518	1.184	0.884 to 1.585	1.119	0.645 to 1.943
High school certificate	1.342†	1.005 to 1.792	1.406†	1.005 to 1.966	0.929	0.486 to 1.776
> High school level	1.402†	1.062 to 1.850	1.524†	1.087 to 2.137	0.930	0.495 to 1.749
Occupational group at diagnosis						
Farmers, manual workers	0.797	0.607 to 1.046	0.901	0.627 to 1.295	0.717	0.411 to 1.249
Others	1					
Work contract at cancer diagnosis						
Permanent	0.889	0.711 to 1.112	0.756†	0.579 to 0.988	1.617§	0.965 to 2.708
Others	1		1			
Income per person in the household at diagnosis (Euros)	1.106	0.933 to 1.310	1.043	0.846 to 1.285	1.286	0.875 to 1.888
Tumor type						
Colon/rectum	1		1			
Breast	0.900	0.625 to 1.297	1.034	0.626 to 1.707		
Prostate	1.437	0.857 to 2.412	1.040	0.558 to 1.941		
Upper aerodigestive tract/lung	0.705	0.453 to 1.097	0.742	0.342 to 1.607	0.748	0.288 to 1.942
Malignant hemopathy	0.630§	0.375 to 1.057	0.660	0.284 to 1.531	0.599	0.203 to 1.769
Other cancer	0.913	0.652 to 1.280	1.178	0.723 to 1.922	0.405†	0.198 to 0.827
Disease status						
Progressive disease	0.318‡	0.201 to 0.504	0.360‡	0.213 to 0.608	0.650	0.230 to 1.838
Nonprogressive disease	1		1			
Prognosis index	2.847‡	1.591 to 5.097	3.346‡	1.639 to 6.833	0.620	0.181 to 2.130
Treatment						
Surgery	1		1			
Treatment including chemotherapy	0.683‡	0.549 to 0.851	0.746†	0.567 to 0.982	0.706	0.439 to 1.133
Other treatment	0.761	0.504 to 1.149	1.120	0.581 to 2.160	0.503	0.211 to 1.199
Side effects						
None or only slightly disturbing	1		1			
Yes, rather disturbing	0.721‡	0.384 to 0.613	0.534‡	0.406 to 0.702	0.789	0.473 to 1.318
Yes, very disturbing	0.485‡	0.605 to 0.858	0.703‡	0.576 to 0.859	1.227	0.817 to 1.843
Life priorities since the diagnosis						
Attach more importance to their personal lives life	0.799†	0.672 to 0.951	0.750‡	0.613 to 0.918	1.196	0.807 to 1.772
Attach equal importance to their personal lives and their work	1		1			
Attach more importance to their work	1.228	0.843 to 1.789	1.151	0.732 to 1.812	1.320	0.585 to 2.980
Intercept	2.900‡	1.520 to 4.280	2.997‡	1.360 to 4.635		
Weibull parameter‖	1.147‡	1.063 to 1.232	1.169‡	1.083 to 1.255		
Log-likelihood	1,879		1,864			

Abbreviations: AF, accelerating factor; LR, likelihood ratio.

*Calculated as exp(-β) and interpreted as a hazard ratio. For instance, in model 1, men (AF = 1.292) are 29.2% more likely to return to work than women (the reference category) at each point in time. Likewise, in model 1, if a patient has a progressive disease, then the model predicts that the risk of return to work after sick leave will decrease (AF = 0.318) in comparison with patients whose disease is not progressive (the reference category). This is interpreted as a 68.2% decrease in the probability of return to work after sick leave.

†Significant at 5%.

‡Significant at 1%.

§Significant at 10%.

‖Indicates whether the risk increases (> 1) or decreases (< 1) with the duration of the sick leave.

disturbing adverse effects; AF = 0.534, $P < .001$ for very disturbing adverse effects). Progression of the disease at the time of the interview was also found to delay RTW (AF = 0.360, $P < .001$). Overall, time to RTW depended on the prognosis of the disease (AF = 3.346, $P < .001$).

Some sociodemographic and psychosocial factors were also found to be related to the RTW process. Higher educational levels accelerated RTW (AF = 1.406, $P = .045$ for those with secondary school education and AF = 1.524, $P = .014$ for those with higher educational levels). People with a permanent work contract showed longer duration of sick leave than employees with fixed-term contracts and self-employed workers (AF = 0.756, $P = .042$). In addition, those who focused more strongly on their personal lives delayed their RTW (AF = 0.750, $P = .006$).

Two variables were found to explain sex differences in the RTW process. Older men returned significantly more slowly to work than women (AF = 0.970, $P = .013$). Otherwise, married men returned to work significantly much faster than married women (AF = 1.866, $P = .019$).

Duration Dependence of RTW After Sick Leave

The Weibull parameter allowed us to test whether the probability of RTW after sick leave during the 2-year period depended on time elapsing on sick leave. The value of this parameter differs significantly between men and women, as confirmed by the nonoverlapping CIs (Table 3). In men, the value of this parameter did not differ significantly from 1, indicating that the conditional probability of return to work is constant over time. This was not so in the case of women, in whom a significant positive duration dependence was observed (Weibull parameter >1, $P < .001$), which means that the conditional probability of RTW increased with the time spent on sick leave. Finally, an LR test comparing model 3 with model 2 (see bottom of Table 3) supported the relevance of estimating sex-specific duration dependence.

DISCUSSION

Considerable importance is being attached these days to the workplace consequences of cancer, as increasing numbers of people of working age are being diagnosed with cancer. The predictors of RTW after sick leave were studied here among cancer survivors 2 years after diagnosis, focusing on the sex-related differences between these predictors. The question of duration dependence was also addressed, assuming that the time spent away from work (the sick leave period) determines patients' chances of returning to work after sick leave. This is one of the main advantages of the AFT model over Cox's model (Appendix). Few studies have dealt so far with RTW among patients with cancer using survival models, and only one study has been published to date in which an AFT model was used to explain RTW patterns of patients with cancer.[17] The latter study did not include clinical data on points such as cancer stage, types of treatment, or adverse effects. One of the strengths of the present study is the fact that several clinical variables were available, which were included in our survival analysis.

In our study, an AFT Weibull model was used to deal with duration dependence. This approach made it possible to analyze whether time itself can be said to be an explanatory variable in the duration of RTW after sick leave. We expected to find a negative duration dependence, where the probability of returning to work after sick leave decreases as the duration of sick leave increases, as suggested by previous studies.[16,17,24] We found that the RTW rates of men and women depended differently on the time elapsed in sick leave. In the case of women, the conditional probability of RTW increased with the time spent on sick leave. A possible explanation is that, compared with men, there may be smaller differences between women's wages and the compensation provided by the National Health System, as in France, the sex wage gap disfavors women, ceteris paribus. This could reduce women's incentive of returning to work faster than men.[25] In this case, as suggested in a study carried out in the field of labor economics,[26] women's utility of returning to work may be lower than the utility of staying in sick leave. Unfortunately, in our survey, participants were asked about the household income rather than the individual wage, and this hypothesis cannot be statistically confirmed. Notice that it could also explain the fact that women were more likely than men to go on sick leave (Table 1).

The analysis of duration dependence showed that the duration of sick leave is a sex-specific process. This was confirmed by the results of the multivariate analysis including a sex interaction. Thus men living with a spouse had a faster RTW after sick leave. Most of these men were probably aware of their economic responsibilities to their family, which gave them an incentive to return to work as soon as possible. If an older age is a well-known predictor of RTW, it is not clear why this factor was sex-specific in our case.

Table 3. Weibull Parameter Predicting Return to Work After Sick Leave

	Model 3: Model Stratified by Sex			
	Men (n = 257)		Women (n = 544)	
Variable	Coefficient	95% CI	Coefficient	95% CI
Weibull parameter*	1.036	0.899 to 1.017	1.243†	1.133 to 1.354
Log-likelihood	519		1,342	
LR test				
Model 3 *v* model 1 (df = 20)	36 to be compared with $\chi^2(20) = 31.41$ at 5%			
Model 3 *v* model 2 (df = 1)	6 to be compared with $\chi^2(1) = 3.84$ at 5%			

Abbreviations: AF, accelerating factor; df, degrees of freedom; LR, likelihood ratio.
*Indicates whether the risk increases (> 1) or decreases (< 1) with the duration of the sick leave.
†Significant at 1%.

Finally, this study confirmed strong evidence that various factors, other than sex, play a role in cancer survivors' RTW process. Hence progressive disease, receiving chemotherapy, and perception of adverse effects decelerated RTW, in accordance with previous studies.[6,15,27-29] Survivors in the higher educational group were more likely to accelerate their RTW. We can hypothesize that for these patients, as job satisfaction or the possibility of achieving career goals probably play a role.[30-32] Another important finding was that cancer seemed to produce a reassessment of life goals, with people probably placing greater emphasis on their familial life and attaching less value to work than they did 2 years before. This point has been mentioned in the literature in regard to changes in life values linked with the experience of a mortal disease.[33-35]

Along with the methodologic improvement obtained using a Weibull survival model, one of the strengths of our study was the fact that it involved quite a large population-based national sample, representing the whole population of patients with cancer 2 years after diagnosis. In addition, although many studies on cancer survival have included patients at different times after diagnosis, the present study dealt with cancer survivors during the same 24-month period, thus preventing the existence of any confounding effects between cancer and technological and medical innovations, or changes in the labor market, work legislation, or social protection. One should be careful about extending our findings to other countries, as the RTW process is closely linked to the sick-leave system. In the case of France, where the legislation gives workers considerable protection, and in most Western European countries, there are no job-lock problems, whereas the job-lock situation is certainly a major predictor of RTW in less generous sick-leave systems such as that of the United States.

Despite the advantage of dealing with a population-based national sample, this study has several limitations. First, although quite a high response rate was obtained (64.1%), it is likely that those who did not respond may have had different characteristics from those who did. We know in particular that the nonrespondents were older and that a larger percentage of them were diagnosed with breast cancer. Second, the retrospective nature of the study may have induced a memory distortion and reinterpretation bias. However, some studies have shown that when people are interviewed retrospectively after a traumatic event such as cancer,[36] there is little memory bias; this is all the more true in the case of the present study, in which the time elapsing between diagnosis and the interview (2 years) was relatively short. Third, 274 people were no longer employed in 2004 and were not included in the study because of unknown information about their sick leave. Fourth, no data were collected on the cancer survivors' comorbidities, although this factor may have affected their RTW patterns. However, only patients younger than 60 years were included, and it has been established that people in this age group have significantly fewer comorbidities than those older than 60 years.[37]

Finally, we could not analyze the workplace adjustments, such as changes in the work schedule or working hours, occurring after sick leave for cancer. However, only 0.8% of the men and 1.2% of the women in our sample shifted to part-time jobs. Because of these low proportions, this variable was not included in our model.

Despite these limitations, this is the first time to our knowledge that the combined effects of medical, sociodemographic, economic, and psychosocial variables on RTW after sick leave have been analyzed in such a large sample using an AFT model. The results obtained show that the duration of sick leave is sex-specific. This difference in the RTW process between men and women is probably mostly due to the different duration dependences. However, other factors such as age and marital status affect the RTW process differently for men and women. A better knowledge of the RTW process would enable physicians to identify patients with intervention needs more accurately, thus helping national implementation of more cost-effective strategies for managing cancer survivors' RTW.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Laetitia Malavolti, Anne-Gaelle Le Corroller-Soriano
Collection and assembly of data: Laetitia Malavolti
Data analysis and interpretation: Patricia Marino, Luis Sagaon Teyssier, Anne-Gaelle Le Corroller-Soriano
Manuscript writing: All authors
Final approval of manuscript: All authors

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ORIGINAL REPORT

Effect of Ruxolitinib Therapy on Myelofibrosis-Related Symptoms and Other Patient-Reported Outcomes in COMFORT-I: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Purpose
To assess the effects of ruxolitinib on symptom burden and quality of life (QoL) and to evaluate the ability of the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 to measure meaningful changes in myelofibrosis-related symptoms in patients with myelofibrosis.

Patients and Methods
COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment–I) is a double-blind, placebo-controlled phase III study evaluating ruxolitinib in patients with intermediate-2 or high-risk myelofibrosis. Exploratory analyses were conducted on the following patient-reported outcomes (PROs) assessments: modified MFSAF v2.0 (individual symptoms and Total Symptom Score [TSS]), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale, and Patient Global Impression of Change (PGIC).

Results
Patients receiving ruxolitinib experienced improvements in individual myelofibrosis-related symptoms, although patients receiving placebo experienced worsening ($P < .001$). The majority (91%) of ruxolitinib-treated patients designated as ≥ 50% TSS responders (≥ 50% TSS improvement) self-reported their condition as either "Much improved" or "Very much improved" on the PGIC. These patients achieved significant improvements in the EORTC QLQ-C30 functional domains and Global Health Status/QoL versus patients receiving placebo, who experienced worsening on these measures ($P \leq .0135$). Ruxolitinib-treated patients with a lesser degree of symptom improvement (< 50% TSS responders) also achieved improvements over placebo on these measures. The degree of spleen volume reduction with ruxolitinib correlated with improvements in TSS, PGIC, PROMIS Fatigue Scale, and EORTC Global Health Status/QoL. Ruxolitinib-treated patients who achieved a ≥ 35% reduction in spleen volume experienced the greatest improvements in these PROs.

Conclusion
Ruxolitinib-treated patients achieved clinically meaningful improvements in myelofibrosis-related symptoms and QoL, but patients receiving placebo reported worsening of symptoms and other PROs.

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INTRODUCTION

Myelofibrosis is characterized by splenomegaly,[1] cytopenias,[1] and symptoms that may be debilitating, such as fatigue, pruritus, night sweats, fever, bone pain, and weight loss.[2] These symptoms are highly prevalent among patients with myelofibrosis and can adversely affect quality of life (QoL).[2] The presence of myelofibrosis-related constitutional symptoms (unexplained fever, drenching night sweats, weight loss) has been identified as a risk factor for shortened survival.[3] Splenomegaly and myelofibrosis symptoms are thought to be driven by dysregulation of the Janus kinase (JAK) –STAT pathway resulting from mutations that lead to constitutively active JAK2[4,5] or increased proinflammatory cytokines that signal through JAK1 and JAK2.[6]

There are many types of patient-reported outcome (PRO) tools used in oncology; until recently, none were specifically designed to evaluate the symptoms of myelofibrosis.[7] The Myelofibrosis Symptom Assessment Form (MFSAF) was developed to evaluate the presence and severity of myelofibrosis-related symptoms.[7] In a phase II study of patients with myelofibrosis treated with ruxolitinib, a JAK1/JAK2 inhibitor, the MFSAF proved sensitive to ruxolitinib-associated improvements in symptoms over time, and symptom improvements correlated with objective measures of efficacy.[8] Subsequently, a more streamlined version of the MFSAF, the modified MFSAF v2.0, was developed and was used in a phase III, double-blind, placebo-controlled study (COMFORT-I; Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment–I).[9] In this analysis, we evaluated the ability of the modified MFSAF v2.0 to measure meaningful changes in myelofibrosis-related symptoms and the effects of ruxolitinib on symptom burden and other PROs in COMFORT-I.

PATIENTS AND METHODS

Patients

Adult patients who were diagnosed with primary myelofibrosis, postpolycythemia vera myelofibrosis, or postessential thrombocythemia myelofibrosis[10]; were classified as International Prognostic Scoring System[3] high risk or intermediate 2 risk; had palpable splenomegaly ($\geq$ 5 cm below left costal margin); and were resistant or refractory to, intolerant of, or not candidates for available therapy (in the investigator's opinion) were enrolled. Full inclusion and exclusion criteria have been previously reported.[9]

Study Design

In this multicenter, double-blind phase III trial, patients were randomly assigned 1:1 to receive placebo or ruxolitinib (starting doses of 15 mg twice daily for platelet counts 100 to 200 $\times$ 10^9/L and 20 mg twice daily for platelet counts $>$ 200 $\times$ 10^9/L). Dose modification occurred in a blinded fashion for both arms on the basis of predefined criteria. Dose increases for lack of efficacy were permitted, and dose reductions for declining platelet or absolute neutrophil counts were required. The minimum recommended dose was 5 mg twice per day and the maximum permitted dose was 25 mg twice per day.[9] Before week 24, patients receiving placebo were eligible for early unblinding and crossover to ruxolitinib if they had a $\geq$ 25% increase from baseline in spleen volume along with worsening early satiety accompanied by weight loss or worsening splenic pain with increased narcotic requirements. After week 24, patients receiving placebo with asymptomatic spleen growth $\geq$ 25% could also cross over to ruxolitinib. The primary end point was the proportion of patients who achieved a $\geq$ 35% reduction in spleen volume by magnetic resonance imaging or computed tomography scans from baseline to week 24. The comparative secondary end point controlled for type I error was the proportion of patients who achieved $\geq$ 50% reduction (improvement) in the Total Symptom Score (TSS) from baseline to week 24 by using the modified MFSAF v2.0 electronic diary.[9]

This study was conducted in accordance with local regulatory requirements and Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent.

PRO Assessments

The PRO measures used in the COMFORT-I study have been previously described in detail[9]; a brief overview is provided here.

Modified MFSAF v2.0 and TSS

The modified MFSAF v2.0, an electronic daily symptom diary, was developed for the COMFORT-I study on the basis of prior paper versions of myelofibrosis symptom assessment forms[7,8] along with feedback from the US Food and Drug Administration. Patients completed the modified MFSAF v2.0 every night from baseline through week 24 (25 weeks total) with electronic data downloaded to a central server. Patients rated the following myelofibrosis symptoms, at their worst as experienced in the 24 hours before assessment, by using a scale from 0 (absent) to 10 (worst imaginable): night sweats, pruritus/itching, abdominal discomfort, pain under the ribs (left side), early satiety, bone/muscle pain, and inactivity. The TSS reflects the sum of the scores of these symptoms except inactivity, for a maximum possible score of 60 (ie, most severe symptom experience). The baseline TSS was the average of seven daily measurements before baseline (at least four of which had to be non-missing), and the week 24 TSS was the average of 28 daily measurements before week 24 (at least 21 of which had to be non-missing).

PGIC Scale

The Patient Global Impression of Change (PGIC) scale assessed patients' perceptions of change in their myelofibrosis symptoms over time. The PGIC has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial.[11] In this study, patients answered the following question at monthly study visits beginning at week 4: "Since the start of the treatment you've received in this study, your myelofibrosis symptoms are (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, (7) Very much worse."

EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) is a 30-item questionnaire used to evaluate QoL and includes five functional domains (physical, cognitive, role, emotional, and social) and a global health status scale. Each subscale is evaluated on a standardized scale of 0 (worst) to 100 (best).[12] Patients completed the EORTC QLQ-C30 at the baseline visit and at each study visit.

PROMIS Fatigue Scale: Short Form

This scale measures the frequency and impact of fatigue.[13] The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale contains seven items with a recall period of 7 days. Each of the items uses a 5-point response option with scores of 1 (never) to 5 (always). An average score is calculated and transformed to a final score on a 100-point scale ranging from 0 (never fatigued) to 100 (always fatigued). Patients completed the instrument at the baseline visit and at each study visit.

Statistical Analysis

Patient disposition and baseline PRO scores were summarized descriptively. Percent changes from baseline in individual symptom scores (average symptom scores from the previous 28 days, as measured by the modified MFSAF v2.0), EORTC QLQ-C30 subscale scores and PROMIS Fatigue Scale scores were calculated at weeks 4, 8, 12, 16, 20 (individual symptom scores only), and 24. Treatment comparisons (ruxolitinib *v* placebo) in these percent changes were performed by using Wilcoxon rank sum test at each time point. Percent changes were calculated at the patient level before descriptive statistics were derived.

Previous data[14] suggested that ruxolitinib doses as low as 10 mg twice per day were associated with symptom benefits similar to those of higher doses in patients with myelofibrosis. To confirm this, we also assessed the effect of dose on symptom improvements. Median percent change from baseline in TSS at week 24 was calculated across groups on the basis of final titrated ruxolitinib dose at week 24 (average ruxolitinib dose during weeks 21 to 24). Median percent change from baseline in TSS at week 24 in ruxolitinib-treated patients with and without new onset/worsening of grade 3 to 4 anemia or grade 3 to 4 thrombocytopenia were also calculated. These TSS analyses were descriptive.

The relationships between the following variables were also evaluated: (1) improvement in TSS ($\geq$ 50% or $<$ 50% TSS response) with the PGIC score and change from baseline in EORTC QLQ-C30 scores at week 24 and (2) spleen volume reductions ($<$ 10%, 10% to 35%, $\geq$ 35%) with the PGIC, percent change from baseline in TSS, and changes from baseline in PROMIS Fatigue Scale and EORTC QLQ-C30 Global Health Status/QoL scores at week 24. For the relationship between TSS response and EORTC QLQ-C30 subscale score, an analysis of covariance was used with the baseline EORTC QLQ-C30 subscale as the covariate, the TSS response as the main effect, and the all-placebo group as the reference level for comparisons. For the relationship between spleen volume reduction and improvement on the PROs, analysis

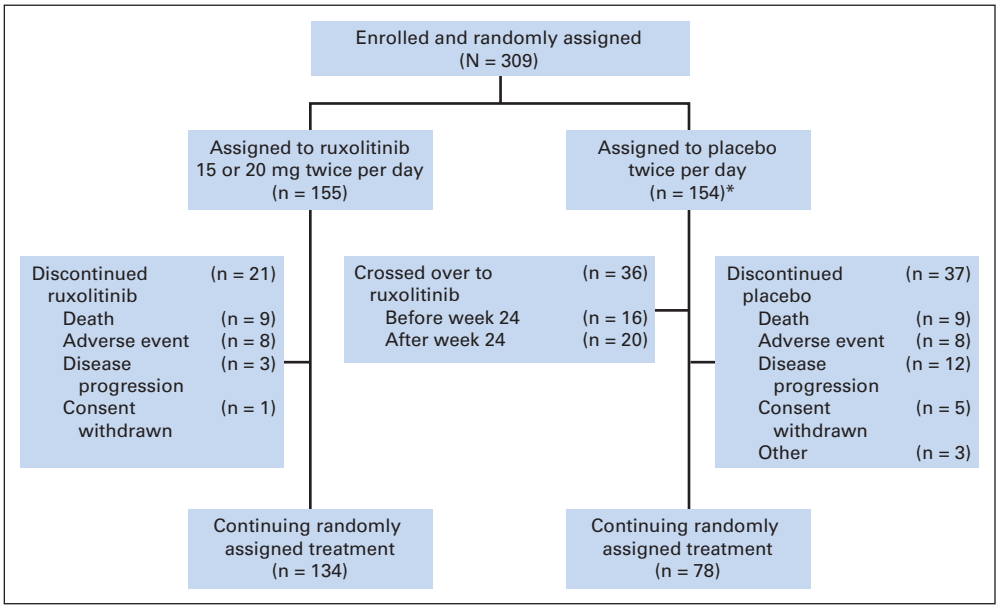

Fig 1. CONSORT diagram illustrating the disposition of the 309 enrolled patients at the time of primary analysis data cutoff. (*) Three patients not evaluable for safety but included in the intent-to-treat analysis of efficacy.

of covariance was used with the baseline value as the covariate, the spleen volume reduction group as the main effect, and with the all-placebo group as the reference level for comparisons. Because these analyses were exploratory and descriptive, no adjustments were made for multiple comparisons. These analyses were based on observed data (no missing value imputation was performed).

The interpretability of the modified MFSAF v2.0 was explored as described in the Appendix (online only). Test-retest reliability between week 7 and week 8 was measured by using intraclass correlation coefficients.

RESULTS

Patient Disposition and Baseline PRO Measures

Patient disposition (N = 309) at the time of the primary analysis, when all patients completed at least 24 weeks of treatment or discontinued and at least half the remaining patients completed 36 weeks of treatment, is shown in Figure 1. As reported previously, baseline characteristics were generally similar in the two treatment arms.[9] The primary and secondary efficacy end points were also previously reported.[9] Briefly, by week 24, a significantly greater proportion of ruxolitinib-treated patients had a $\geq$ 35% reduction in spleen volume compared with patients in the placebo group (41.9% *v* 0.7%; odds ratio, 134.4; 95% CI, 18.0 to 1,004.9; $P < .001$).[9] Ruxolitinib treatment also provided improvement in symptom burden, with 45.9% of patients achieving a $\geq$ 50% reduction in TSS from baseline to week 24 versus 5.3% of the placebo arm (odds ratio, 15.3; 95% CI, 6.9 to 33.7; $P < .001$).[9] Only 3.9% of ruxolitinib-treated patients showed a significant worsening of TSS from baseline to week 24 (ie, > 50% increase in TSS) compared with 33.0% of patients receiving placebo.

The majority of patients completed the EORTC QLQ-C30, PGIC, and PROMIS Fatigue Scale at each study visit (Appendix Table A1, online only), and the electronic daily data capture for the modified MFSAF v2.0 resulted in high compliance rates for completion of this PRO and almost no missing data. Completion of the electronic daily diary required 1 minute or less for 94% of patients, and test-retest reliability intraclass correlation coefficients (week 7 to week 8) were 0.97 for patients treated with placebo and 0.98 for patients treated with ruxolitinib.

Mean scores at baseline in the PRO measures were similar between treatment groups (Table 1). Moreover, all individual myelofibrosis-related symptoms assessed by the modified MFSAF v2.0 were prevalent in the majority of patients in the COMFORT-I study population at baseline. The most prevalent symptoms (reported by > 90% of patients receiving ruxolitinib and placebo) were abdominal discomfort, early satiety, and inactivity. Of note, these same symptoms ranked greatest in severity (Fig 2). EORTC QLQ-C30 subscales reflected poor QoL at baseline and were similar to scores of other populations with advanced cancer and another patient population with myeloproliferative neoplasms.[15,16] Of the five functional domains, patients suffered the greatest burden in role functioning.

Changes in Individual Myelofibrosis-Related Symptoms, QoL, and Fatigue

Overall, individual symptom scores as assessed by the modified MFSAF v2.0 at each 4-week time point in patients receiving ruxolitinib showed improvement relative to baseline (Fig 3). There was approximately linear worsening in symptom scores for patients receiving placebo over the entire 24 weeks. The differences between ruxolitinib- and placebo-treated groups were significant at all time points for all symptoms ($P < .001$; Fig 3). Improvements relative to baseline and placebo in PROMIS Fatigue Scale score and most EORTC QLQ-C30 subscales were also seen with ruxolitinib treatment (Appendix Table A2, online only).

Improvement in TSS by Average Total Daily Ruxolitinib Dose and Effect of Anemia or Thrombocytopenia on TSS in Ruxolitinib-Treated Patients

Although patients in the study began dosing at either 15 or 20 mg twice per day, individualized dose optimization resulted in an overall average dose exposure for ruxolitinib-treated patients of 15.5 mg twice per day. Median improvements from baseline at week 24 in TSS

Table 1. Baseline Scores on Patient-Reported Outcome Measures

Parameter Measured	Ruxolitinib Mean	Ruxolitinib Range	Placebo Mean	Placebo Range	Maximum Score Possible
Modified MFSAF v2.0, TSS	18.2	0-50.1	16.9	0-52.7	60 (worst possible)
EORTC QLQ-C30 Subscales					
Global Health Status/QoL	52.7	0-100	52.9	0-100	100 (best possible)
Physical Functioning	69.7	0-100	67.2	20-100	100 (best possible)
Role Functioning	64.5	0-100	63.2	0-100	100 (best possible)
Emotional Functioning	73.3	0-100	75.5	0-100	100 (best possible)
Cognitive Functioning	80.7	0-100	80.1	16.7-100	100 (best possible)
Social Functioning	68.0	0-100	66.1	0-100	100 (best possible)
PROMIS Fatigue Scale	43.7	10.7-85.7	43.3	0-89.3	100 (worst possible)

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MFSAF, Myelofibrosis Symptom Assessment Form; PROMIS, Patient Reported Outcomes Measurement Information System; QoL, quality of life; TSS, Total Symptom Score.

exceeding 50% were observed for all dose groups in which the dose was ≥ 10 mg twice per day: 71.1% (n = 30), 59.6% (n = 23), 67.7% (n = 38), and 66.2% (n = 20) for dose groups of 10 mg twice per day, 15 mg twice per day, 20 mg twice per day, and 25 mg twice per day, respectively. Ruxolitinib-treated patients who developed new-onset or worsening of grade 3 or 4 anemia achieved TSS improvements at week 24 that were similar in magnitude to improvements in those who did not experience grade 3 or 4 anemia (median, −46.4% [n = 47] and −58.3% [n = 82], respectively). Ruxolitinib-treated patients with and without new-onset or worsening of grade 3 or 4 thrombocytopenia also experienced TSS improvements (median, −26.8% [n = 13] and −62.5% [n = 116], respectively). Although there was an apparent difference in the magnitude of the improvements between these groups, the number of patients with grade 3 or 4 thrombocytopenia was too small to draw a clear conclusion. In contrast, patients receiving placebo showed worsening TSS scores (median, 14.6% [n = 103]).

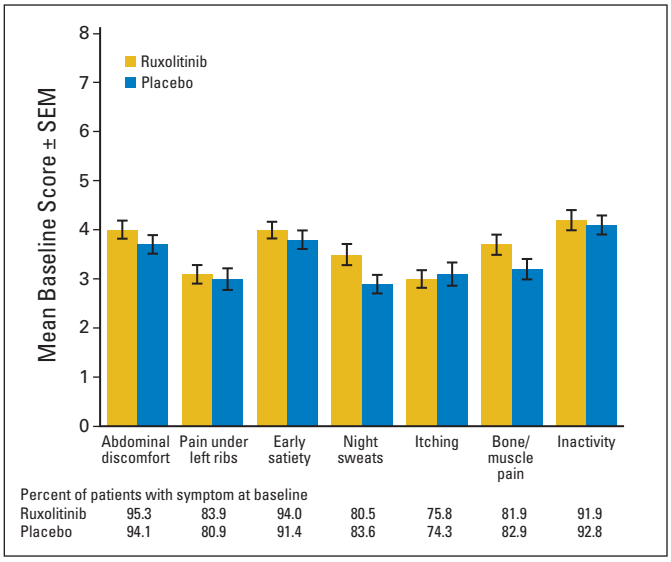

Fig 2. Individual symptom scores at baseline (in patients with symptoms at baseline) as measured by the modified Myelofibrosis Symptom Assessment Form v2.0. The most prevalent symptoms (reported in > 90% of patients in both treatment groups) and most severe symptoms were abdominal discomfort, early satiety, and inactivity. Scale range: 0, absent to 10, worst imaginable.

Relationship Between TSS Improvement and PGIC

As detailed in Table 2, 62 (91.2%) of ruxolitinib patients who were ≥ 50% TSS responders characterized their condition as either "Much improved" or "Very much improved." In addition, 67 (73.7%) of the placebo group who were less than 50% TSS responders characterized their condition as "unchanged" or "worsening." These results suggest a relationship between the TSS and the PGIC in that the individual patient perceived and reported meaningful benefit from the treatment in terms of an overall improvement in myelofibrosis symptoms, which further supports the use of the modified MFSAF v2.0.

Relationship Between TSS Improvement and EORTC QLQ-C30

For each subscale of the EORTC QLQ-C30, ruxolitinib-treated patients reported increases (improvements) from baseline, whereas patients receiving placebo reported decreases (worsening). Ruxolitinib-treated patients defined as ≥ 50% TSS responders achieved significantly greater improvements in the EORTC QLQ-C30 subscales versus patients receiving placebo who continued to show deterioration in their QoL ($P \leq .0135$; Fig 4). Notably, ruxolitinib-treated patients with a lesser degree of symptom response (< 50% TSS responders) also achieved significant improvements over placebo for all EORTC QLQ-C30 subscales ($P \leq .0075$), with the exception of the Emotional Functioning and Cognitive Functioning domains (Fig 4).

Relationship Between Spleen Volume Reductions and PROs

In the ruxolitinib arm, improvements in TSS, abdominal symptoms, nonabdominal symptoms, and the PGIC score correlated with reductions in spleen size; patients who had a ≥ 35% reduction in spleen volume had the greatest improvement in symptoms and perceived change in condition (Figs 5A to 5D). Of note, however, ruxolitinib-treated patients who exhibited even small spleen volume reductions (< 10%) achieved meaningful improvements in these PRO measures compared with patients in the placebo group. In addition, ruxolitinib-treated patients who achieved a ≥ 10% reduction in spleen volume had significant improvements versus placebo in both the PROMIS Fatigue Scale ($P < .001$; Fig 5E) and EORTC QLQ-C30 Global Health Status ($P < .001$; Fig 5F). Indeed, the improvements in

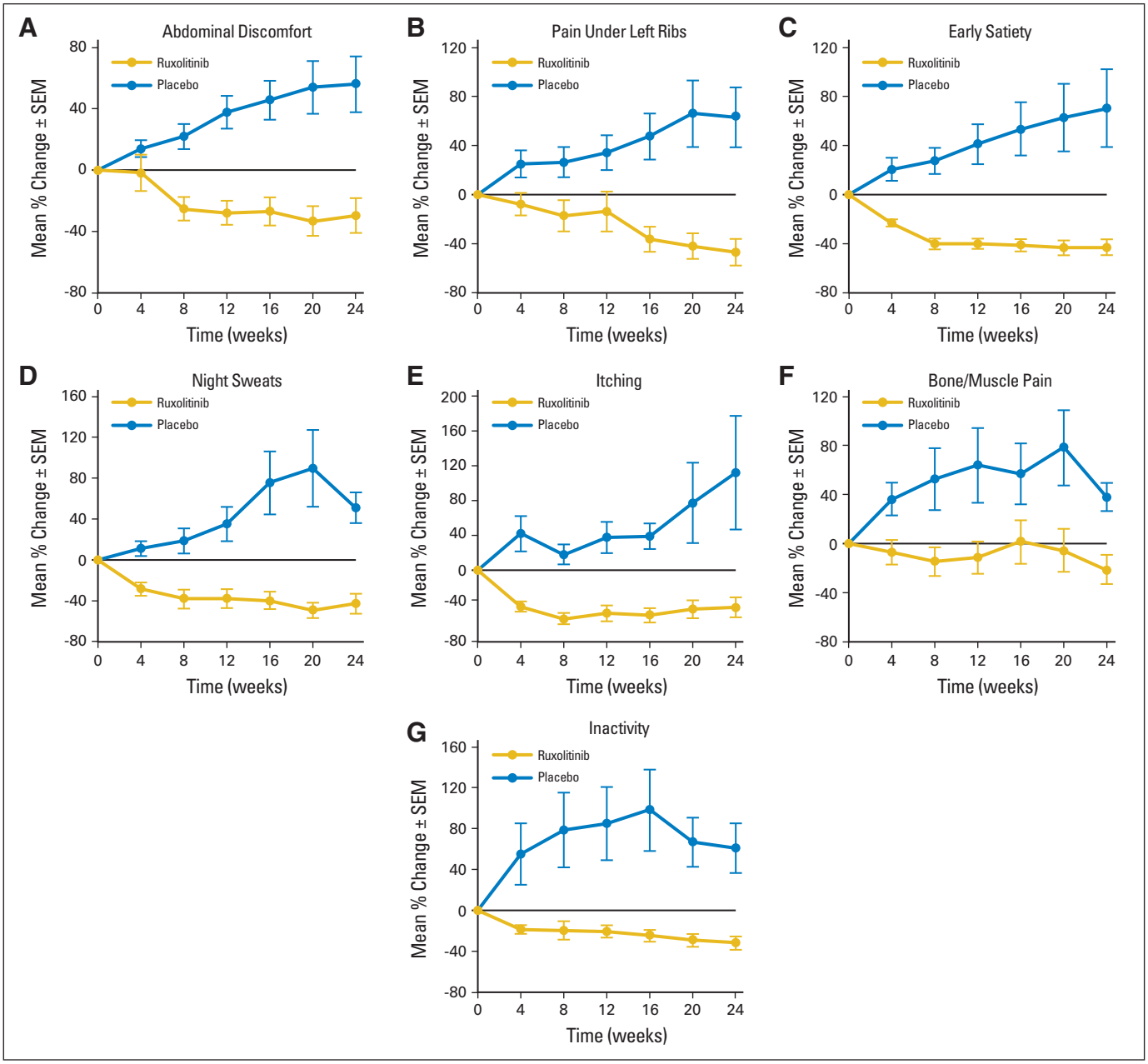

Fig 3. (A-G) Assessment of individual symptom burden by using the modified Myelofibrosis Symptom Assessment Form v2.0. Individual symptom scores at each 4-week time point improved in patients receiving ruxolitinib, whereas patients who received placebo experienced a worsening of symptoms. $P < .001$ for all comparisons between ruxolitinib and placebo at all time points (weeks 4, 8, 12, 16, 20, and 24). Individual symptom scores at each 4-week time point were calculated by averaging the daily individual symptom scores from the previous 28 days.

PRO parameters for ruxolitinib-treated patients who achieved ≥ 35% reduction in spleen volume versus those who achieved a 10% to less than 35% reduction in spleen volume were not significantly different (all $P \geq .07$).

DISCUSSION

In this randomized, placebo-controlled study, patients showed a high prevalence and severity of individual myelofibrosis-related symptoms at baseline, and the modified MFSAF v2.0 was sensitive to differentiating responses in the placebo and ruxolitinib arms over time. Individual symptom scores with ruxolitinib showed improvement relative to baseline and to placebo early in the course of study treatment. The true magnitude of symptom response within 4 weeks of initiating ruxolitinib therapy may be underestimated in this analysis, because symptom scores calculated by using a 28-day average included scores from the initial days of treatment that may have potentially diluted the benefit seen later in the treatment period. Analysis of TSS in ruxolitinib-treated patients by using a 7-day moving average over time shows that the majority of TSS responses (≥ 50% reduction in TSS

Table 2. Relationship Between PGIC Scale and TSS

	Ruxolitinib* (n = 127)				Placebo* (n = 100)				Total Sample* (N = 227)			
	≥ 50% TSS Responder (n = 68)		< 50% TSS Responder (n = 59)		≥ 50% TSS Responder (n = 9)		< 50% TSS Responder (n = 91)		≥ 50% TSS Responder (n = 77)		< 50% TSS Responder (n = 150)	
PGIC Scale	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Very much improved	35	51.5	8	13.6	1	11.1	0	0.0	36	46.8	8	5.3
Much improved	27	39.7	19	32.2	3	33.3	7	7.7	30	39.0	26	17.3
Minimally improved	3	4.4	22	37.3	3	33.3	17	18.7	6	7.8	39	26.0
No change	0	0.0	6	10.2	2	22.2	30	33.0	2	2.6	36	24.0
Minimally worse	2	2.9	3	5.1	0	0.0	19	20.9	2	2.6	22	14.7
Much worse	1	1.5	0	0.0	0	0.0	14	15.4	1	1.3	14	9.3
Very much worse	0	0.0	1	1.7	0	0.0	4	4.4	0	0.0	5	3.3

NOTE. ≥ 50% TSS responders are patients who achieved a ≥ 50% improvement in modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 Total Symptom Score (TSS; baseline TSS–week-24 TSS); < 50% TSS responders are patients who achieved a < 50% improvement in modified MFSAF v2.0 TSS (baseline TSS–week-24 TSS).
Abbreviation: PGIC, Patient Global Impression of Change.
*Number of patients with a baseline and week-24 TSS and who completed the PGIC at week 24.

relative to baseline) occur within the first 4 weeks of treatment.[9] The nightly recording of symptoms by the patient and electronic data transfers contributed to a high degree of compliance by patients in obtaining symptom data. Overall, the baseline prevalence of symptoms and rapid, clinically meaningful improvements exhibited by ruxolitinib-treated patients are consistent with those from the phase II study, in which a paper-pencil version of the MFSAF was sensitive to detecting early and sustained symptom improvements with ruxolitinib treatment.[8] Meaningful reductions in symptom burden were observed for ruxolitinib doses ≥ 10 mg twice per day,

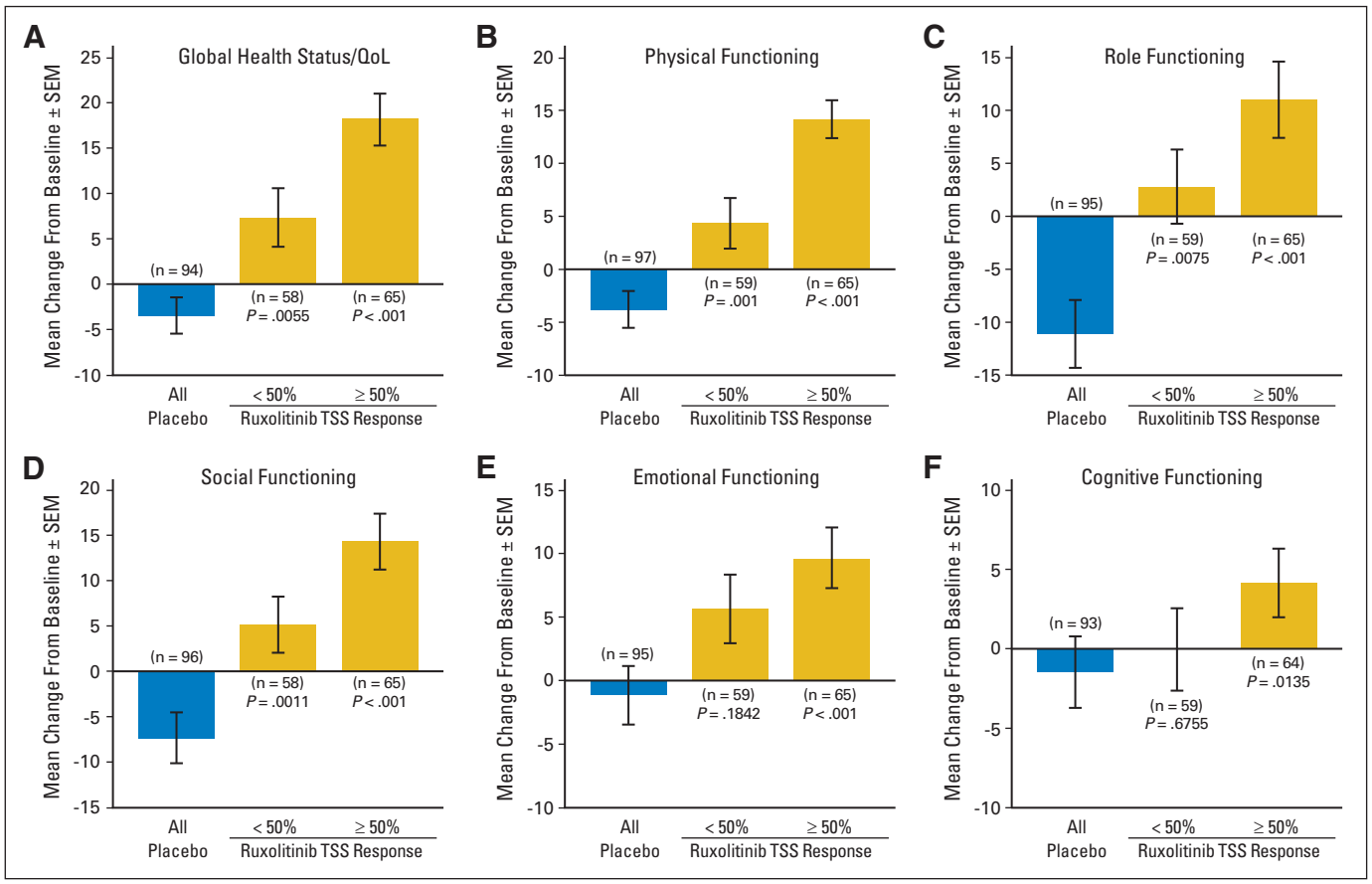

Fig 4. (A-F) Relationship between symptoms as assessed by the modified Myelofibrosis Symptom Assessment Form v2.0, with quality of life (QoL) as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) at baseline. Patients receiving ruxolitinib who were categorized as ≥ 50% Total Symptom Score (TSS) responders achieved significantly greater improvements in the EORTC QLQ-C30 subscales versus patients in the placebo group.

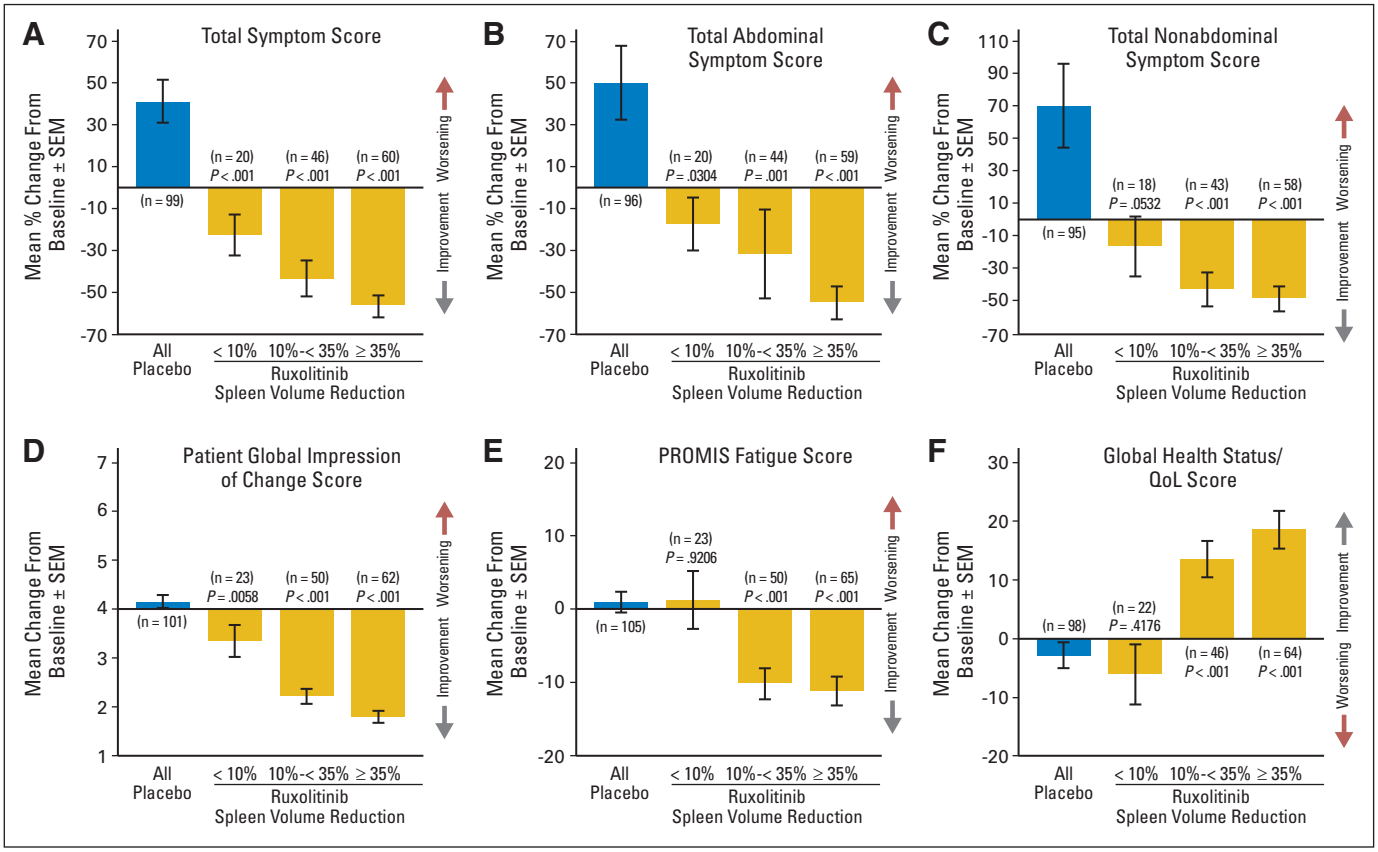

Fig 5. (A-F) Relationship between spleen volume reduction with ruxolitinib and patient-reported outcomes (PROs). Ruxolitinib-treated patients who achieved a ≥ 35% reduction in spleen volume experienced the greatest improvements in all PROs, whereas patients receiving placebo reported worsening of symptoms on these measures. However, patients given ruxolitinib who had ≥ 10% reduction in spleen volume also achieved significant improvements in all PROs. (D) Change from baseline in patient perception of their disease (baseline = score of 4 [no change]). PROMIS, Patient Reported Outcomes Measurement Information System; QoL, quality of life.

while placebo-treated patients reported symptom worsening. Notably, ruxolitinib-treated patients also demonstrated improvement in fatigue (a common symptom in patients with myelofibrosis) relative to baseline and to patients in the placebo group on two PRO instruments.

The modified MFSAF v2.0 was also shown to correlate well with other established PRO assessment tools, including the PGIC and the EORTC QLQ-C30, further supporting use of the MFSAF in patients with myelofibrosis. At baseline, many of the scores for EORTC QLQ-C30 subscales, such as the Global Health Status/QoL, were much lower than those of the general population[15,16] and were consistent with scores for other populations with advanced cancer[15] as well as for another patient population with myelofibrosis.[16] Moreover, the changes in the EORTC QLQ-C30 subscale scores with treatment mirrored trends in the MFSAF, with ruxolitinib ≥ 50% TSS responders showing the most improvement. Even ruxolitinib less than 50% TSS responders demonstrated significant improvements compared with those in the placebo group in EORTC QLQ-C30 subscale scores except for the Emotional Functioning and Cognitive Functioning domains; scores for these two domains were similar between the COMFORT-I population and general population at baseline.[16]

Finally, improvements in symptom burden and perceived change in condition, fatigue, and QoL in ruxolitinib-treated patients were not dependent on reaching the protocol-defined threshold of spleen response (≥ 35% reduction in spleen volume at week 24). Even patients with spleen volume reductions ≥ 10% who received ruxolitinib had significant improvements in symptom burden and perceived change in condition, fatigue, and QoL. A similar finding was observed in the phase II study.[8]

In conclusion, changes in the modified MFSAF v2.0 with ruxolitinib therapy were clinically meaningful. In addition, the modified MFSAF v2.0 correlated well with established PRO measures. Although there was a trend for greater improvements in PROs with greater spleen volume reductions with ruxolitinib, even patients with modest changes in spleen size or symptom scores demonstrated improvements in symptom burden and QoL, whereas patients receiving placebo continued to worsen by these same measures. These data support the use of the MFSAF in clinical studies of treatments for myelofibrosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure

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ORIGINAL REPORT

Curability of Patients With Acute Myeloid Leukemia Who Did Not Undergo Transplantation in First Remission

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See editorial on page 1259 and article on page 1262

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ABSTRACT

Purpose
The aims of this study were to quantify the prospects of salvage treatment of patients who did not undergo transplantation in first complete remission (CR1) and to assess the contribution of allograft in second complete remission (CR2) with respect to major risk groups. This evaluation can inform the decision whether to offer a transplant in CR1.

Patients and Methods
Of 8,909 patients who entered the Medical Research Council AML10, AML12, and AML15 trials, 1,271 of 3,919 patients age 16 to 49 years who did not receive a transplant in CR1 relapsed. Of these patients, 19% are alive beyond 5 years compared with 7% of patients who relapsed after an allograft in CR1. Overall survival and the contribution of a transplant in CR2 were assessed overall and by cytogenetic risk group by using Mantel-Byar analysis.

Results
Fifty-five percent of patients who relapsed entered CR2. This percentage varied by risk group as follows: favorable (82%), intermediate (54%), adverse (27%), and unknown (53%), which resulted in 5-year survivals of 32%, 17%, 7%, and 23%, respectively. Sixty-seven percent of remitters received an allotransplant that delivered superior survival compared with patients who did not receive a stem-cell transplant (42% *v* 16%). A more-stringent assessment of a transplant by using delayed-entry (Mantel-Byar) analysis confirmed the benefit of transplant overall and within intermediate and adverse risk groups but not the favorable subgroup.

Conclusion
Successful salvage treatment of patients who do not undergo transplantation in CR1 and relapse can be achieved in 19% of patients, which is improved by a transplant except in favorable risk disease. This result suggests that, for intermediate-risk patients in particular, equivalent overall survival can be achieved by delaying transplantation until after relapse, which would require many fewer transplants.

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INTRODUCTION

Even after three decades, the question of which patients with acute myeloid leukemia (AML) with a donor should receive an allogeneic stem-cell transplant (SCT) and when this transplantation should occur are still debated. As the most effective antileukemic treatment currently available, the decisions are based on the following three judgments: risk of relapse, risk in first complete remission (CR1) with respect to morbidity or mortality, and prospects for salvage treatment if the patient does relapse. Patients are conventionally stratified into three risk groups (ie, favorable, intermediate, and adverse), usually on the basis of cytogenetics with or without additional molecular information.[1-4] Individual trials and meta-analyses have confirmed that an allogeneic transplant is effective in reducing relapse irrespective of the risk or age group, but the survival benefit is restricted to younger patients (approximately < age 40 years).[5-10] None of these studies were truly randomized but, rather, compared patients with a sibling human leukocyte antigen–matched donor, designated as "donor," with patients who had siblings but without a donor (and also, on occasions, patients with no sibling), designated as "no donor," irrespective of whether or when an SCT was undertaken. Such Mendelian randomization produces comparable groups and is a reasonable substitute for random assignment but cannot allow either for compliance or, indeed, matched nonsibling donor transplants. Only one trial (the United Kingdom

Medical Research Council [MRC] AML12 trial)[11] randomly assigned patients with sibling donors between receipt of chemotherapy and an allograft, and although there was no survival difference, there was relatively poor uptake for this random assignment.

It is generally accepted that patients with favorable risk, on the basis of cytogenetic or *NPM1* mutation status, will not benefit from an SCT as a first-line treatment[12-16] but would still suffer the associated morbidity. The reasons for this lack of benefit are two-fold in that patients have a lower risk of relapse and a high chance of achieving a second remission and effective salvage treatment if they do relapse.

Registry data indicate that the survival of patients who receive an SCT in second remission is 25% to 30%.[17] This survival depends on patient age, cytogenetic risk group, and length of first remission. There is less information on the effect of a strategy of delaying an SCT and only deploying it if a relapse occurs. This concept is important not only to patients, but also concerning the optimal use of the technique in economic, survival, and quality-of-life terms.[18,19] Although registry data provide an indication of what can be expected for patients who actually receive a transplant in second remission, the data do not capture the denominator of patients who relapse. To address this issue, in this study, we examined the outcome of adult patients younger than age 50 years who were entered in the United Kingdom MRC AML10, AML12, and AML15 trials,[20,11,21] did not receive a transplant in first remission, and relapsed. The aim of the study was to quantify the prospects of salvage treatment, with or without an SCT, for such patients who did not undergo transplantation in first remission.

PATIENTS AND METHODS

The AML10, 12, and 15 trials recruited 8,909 patients between 1988 and 2009, of whom 3,919 patients with non–acute promyelocytic leukemia (APL)–AML between age 16 and 49 years are included in this study. Patients had either de novo or secondary AML (defined as AML that was due either to antecedent hematologic disorder or previous chemotherapy treatment). The treatment schedules have been published in detail previously; however, with respect to an allogeneic transplant, the MRC AML10 trial (1988 to 1994) asked whether the addition of a sibling allograft to patients who had already received consolidation therapy was beneficial, including all risk groups. In AML12 (1994 to 2002), patients with core binding factor leukemia were not candidates for a transplant in CR1; the study questioned whether a transplant was superior to chemotherapy as a third or fourth treatment course. In AML15 (2002 to 2009), an SCT could have been used as an alternative to chemotherapy consolidation in standard risk patients but was recommended in high risk disease. Although the three trials asked different transplant questions in different populations (and indeed differed from many trials reported in meta-analyses that evaluated an SCT versus chemotherapy as consolidation and may have had different risk group definitions), the data are combined in this study. The overall survival from a transplant for those who underwent transplantation in CR1 was 64%, with the subgroup outcome shown in Figure 1. Stem cells for an autograft were harvested in CR1. Most patients were exposed to reinduction chemotherapy, which was not protocol prescribed, but was usually anthracycline/cytarabine based. In addition to describing overall outcomes, patients were assessed on the basis of cytogenetic risk by using our previously defined classification.[1] Patients with the *NPM1* mutation were looked at separately. The aims of the study were to define the prospects of salvage treatment of patients overall and in the various risk groups when patients relapsed and to evaluate the role of transplant in the salvage attempt.

End Points and Statistical Analysis

End point definitions followed the guidelines of the International Working Group.[22] Complete remission (CR) and CR with incomplete peripheral blood recovery (CRi) have been combined in this analysis. Relapse and second remission were assessed by the local investigator. Follow-up was complete in March or April 2010, and the median follow-up was 9.2 years (range, 0.2 to 21.9 years).

In any evaluation of a transplant, a direct comparison of overall survival from entry or remission is biased in favor of a transplant because patients who die before receiving a transplant are counted in the no-transplant arm. To counter this zero time shift bias (the transplant group is only at risk from the time of transplant), delayed entry models were used, in which transplant was a time-dependent covariate (ie, patients who received a transplant were included in the transplant group at the time of transplantation). Multivariable analysis was performed by using Cox regression, and univariate analyses were performed by using the Mantel-Byar method.[23] Survival plots were created by using the Kaplan-Meier approach. Unless otherwise stated, survival percentages are Kaplan-Meier estimates at 5 years.

RESULTS

Patient demographics and clinical characteristics of patients are listed in Table 1, and the disposition of patients is shown in Figure 1. Of the 3,919 non-APL patients age 16 to 49 years included in the study, 3,415 patients entered CR or CRi (response rate, 87%). Of these patients, 1,064 patients underwent transplantation in CR1 (548 sibling allografts, 151 allografts from unrelated donors, 245 autografts, 101 reduced-intensity allografts, and 19 transplants of other or unknown type), and 232 patient died in first remission, which left 1,271 patients (60%) who relapsed without transplantation in CR1.

The median duration of CR1 in patients who relapsed without a previous SCT was 9.4 months (range, 0.2 to 120.7 months); the median time to relapse (with death as a competing risk) in this group was 28.5 months. Of the 1,271 patients who relapsed, 168 patients (13%) had favorable risk, 780 patients (61%) had intermediate risk, 108 patients (8%) had adverse risk, and 215 patients (17%) had unknown risk, with a 5-year cumulative incidence of relapse of 34%, 59%, 79%, and 55%, respectively, censored at receipt of an SCT (Fig 2A). Of the 1,271 patients who relapsed, 111 patients underwent transplantation in the first relapse (53 sibling allografts, 25 allografts from matched unrelated donors, 15 autografts, six reduced-intensity transplant, and 12 other types), which resulted in remission in 45% of patients, but the median survival from transplant was 4 months, and the 5-year survival was 9%. This group had a shorter duration of first remission than did patients who did not undergo transplantation in relapse (median remission duration, 6.2 *v* 10.0 months, respectively; $P < .001$); in addition, the median relapse to transplant interval was 56 days. Of the 95 patients with information, 61% received salvage treatment before transplantation; in the remainder of patients, a transplant was given as the first-line salvage treatment. The 1,160 remaining patients were the group focused on in this study, of whom 19% were alive 5 years postrelapse (32% for favorable risk, 17% for intermediate risk, 7% for adverse risk; and 23% for unknown risk; Fig 2B). This survival rate contrasts with the 7% survival rate in patients who relapsed after a CR1 transplant. Overall, of the 1,160 patients, 642 patients (55%) entered CR2, which comprised 133 of 162 patients (82%) with favorable risk, 377 of 702 patients (54%) with intermediate risk, 26 of 97 patients (27%) with adverse risk, and 106 of 199 patients (53%) with unknown risk. Of the 518 patients who did not enter second remission, salvage treatment was given in 73% of cases for which there were data available; patients treated tended to be younger with longer remissions. Of all 642 patients who achieved CR2, 235 patients are alive (5-year

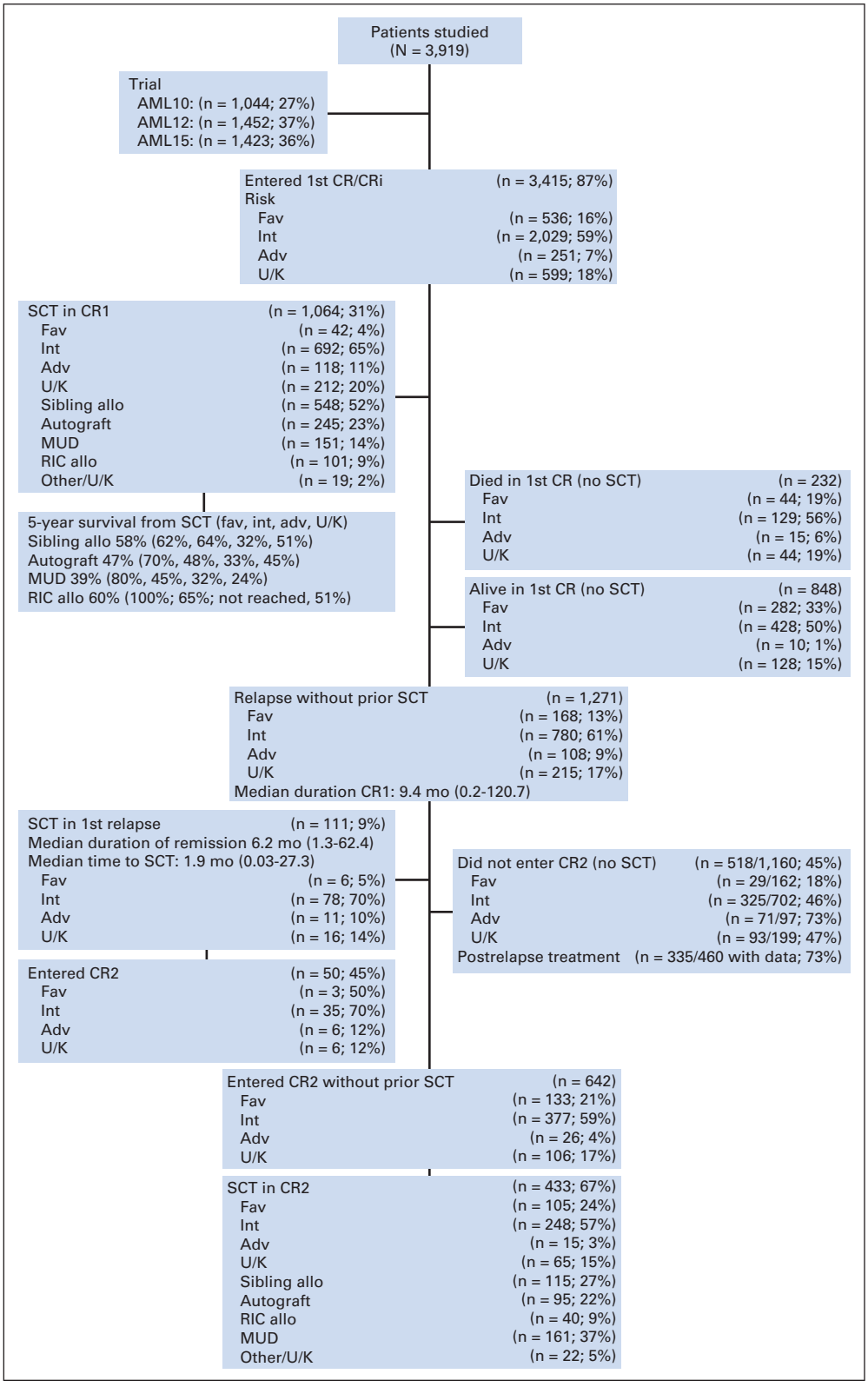

Fig 1. Disposition of patients. Adv, adverse; allo, allograft; CR, complete remission; CRi, CR with incomplete peripheral blood recovery; CR2, second complete remission; Fav, favorable; Int, intermediate; MUD, matched unrelated donor; RIC, reduced-intensity allograft; SCT, stem-cell transplantation; U/K, unknown.

overall survival, 34%). Of the 433 patients (67%) who underwent transplantation, 189 patients are alive (5-year overall survival, 42%), and 46 of the 209 patients who did not undergo transplantation in CR2 are alive (5-year overall survival, 16%). An additional 26 patients underwent transplantation during second relapse or later; these transplants did not contribute to the comparisons. Within risk groups, the respective transplantation rates were as follows: favorable risk, 105 of 133 patients (79%); intermediate risk 248 of 377 patients (66%);

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	All Patients (N = 3,919)		Entering First CR (n = 3,415)		Relapsing Without Previous SCT (n = 1,271)		Entering Second CR Without Previous SCT (n = 642)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Trial								
AML10	1,044	27	859	25	330	26	145	23
AML12	1,452	37	1,278	37	506	40	242	38
AML15	1,423	36	1,278	37	435	34	255	40
Age at entry, years								
16-29	1,047	27	941	28	323	25	182	28
30-39	1,155	29	1,013	30	353	28	191	30
40-49	1,717	44	1,461	43	595	47	269	42
Median	38		37		39		37	
Sex								
F	2,003	51	1,780	52	636	50	322	50
M	1,916	49	1,635	48	635	50	320	50
WHO performance status at entry								
0	1,987	51	1,806	53	636	50	346	54
1	888	23	779	23	321	25	158	25
2	696	18	586	17	224	18	97	15
3	293	7	216	6	78	6	36	6
4	55	1	28	1	12	1	5	< 1
Diagnosis								
De novo	3,677	94	3,235	95	1201	94	622	97
Secondary	242	6	180	5	70	6	20	3
Cytogenetics at entry								
Favorable	559	14	536	16	168	13	133	21
Intermediate	2,246	57	2,029	59	780	61	377	59
Adverse	398	10	251	7	108	8	26	4
Unknown	716	18	599	18	215	17	106	17
WBC at entry ($\times 10^9$/L)								
0-9.9	1,626	42	1,436	43	504	40	253	40
10-49.9	1,290	34	1,153	34	411	33	221	35
50-99.9	442	12	380	11	154	12	81	13
≥ 100	480	13	381	11	181	14	78	12
Unknown	81		65		21		9	
Median	14.0		13.5		16.55		17.3	
FLT3-ITD at entry								
WT	1,166	75	1,013	75	361	69	220	79
Mutant	391	25	346	25	160	31	60	21
Unknown	2,362		2,056		750		362	
NPM1 at entry								
WT	1,008	68	843	66	335	69	185	71
Mutant	469	32	440	34	150	31	76	29
Unknown	2,442		2,132		786		381	
NPM1/*ITD* at entry								
NPM mutant/ITD WT	256	18	243	20	64	14	43	17
NPM WT/ITD WT	815	57	684	55	259	55	154	61
NPM mutant/ITD mutant	210	15	194	16	86	18	33	13
NPM WT/ITD mutant	153	11	124	10	65	14	23	9
Unknown	2,485		2,170		797		389	
Duration of first CR, months	NA		NA					
< 3					132	10	34	5
3-6					220	17	42	7
6-12					471	37	249	39
12-24					298	23	219	34
≥ 24					150	12	98	15
Median					9.4		11.9	

NOTE. Percentages given do not include patients for whom data were not known.
Abbreviations: CR, complete remission; ITD, internal tandem duplication; NA, not applicable; SCT, stem-cell transplant; WT, wild type.

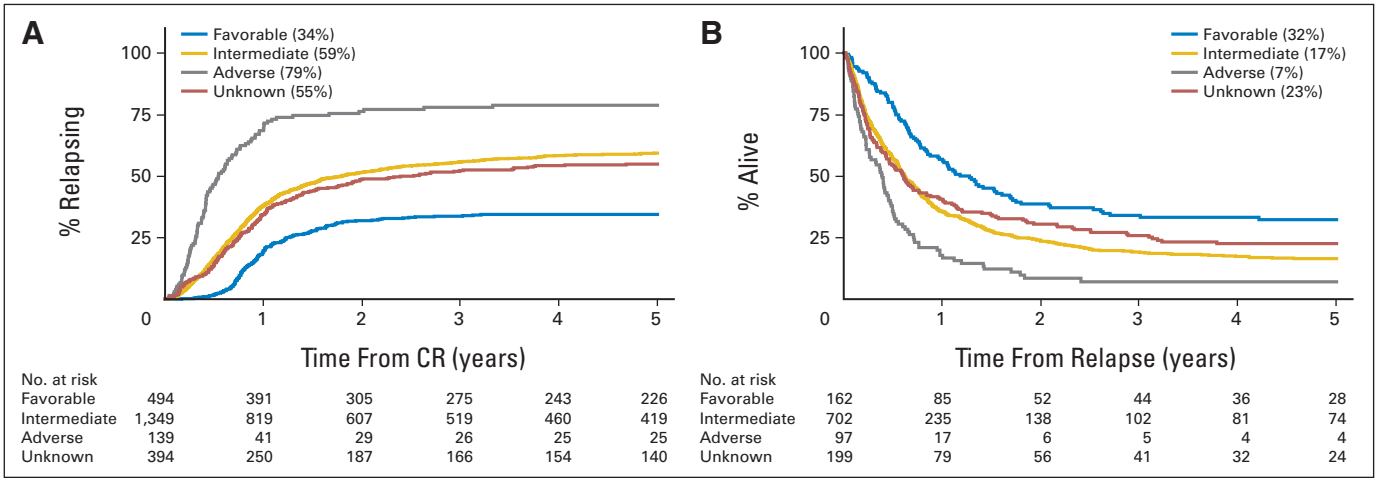

Fig 2. (A) Cumulative incidence of relapse censored at transplantation in first complete remission (CR1). (B) Survival from relapse in patients who did not received a transplant in CR1, excluding a stem-cell transplant in relapse.

adverse risk, 15 of 26 patients (58%); and unknown risk, 65 of 106 patients (61%). The survival rate from a transplant (of any type) is shown in Figure 3.

Contribution of Allograft in CR2 to Survival

Because the intention of this analysis was to quantify the overall salvage rate in patients who did not undergo transplantation in CR1, we also investigated the potential contribution of an allotransplant when delivered in CR2. Of the 433 transplants performed in second remission, there were 115 sibling allografts, 161 allografts from matched unrelated donors, 95 autografts, 40 reduced-intensity transplants, and 22 transplants of other or unknown types.

The median overall survival from an allogeneic transplant in CR2, irrespective of type, was 2.8 years with 40% of patients alive at 5 years. Outcomes by types of allograft indicated that recipients of reduced-intensity allografts had a satisfactory outcome although they were older (Fig 3). There was no difference when the reduced-intensity allograft donor was a sibling (n = 9; 5-year survival: 49%) or unrelated (n = 31; 5-year survival, 38%; $P = .4$), although the numbers were small. Because selection factors that influenced the delivery of a transplant at this stage were likely to have been substantial, a more stringent assessment of the contribution of an allotransplant in CR2 by using Mantel-Byar comparisons was used. For all 314 patients to whom an allograft was delivered, the Mantel-Byar estimate of survival was 44% with a median follow-up of 5.4 years, which was significantly better than the 21% for the 326 patients who did not receive an allograft (Fig 4A). In a multivariate analysis of all allografts (including reduced intensity) and considering the prognostic effect of age, date of recruitment, sex, cytogenetics, performance status, WBC count, duration of first remission (as a continuous variable measured in years), source of cells, and type of transplant (reduced intensity *v* myeloablative), only the duration of CR1 was significantly associated with the outcome, with conditioning type being nonsignificant, although there was some evidence of a worse outcome for patients with an unrelated donor (adjusted hazard ratio, 1.38; $P = .06$).

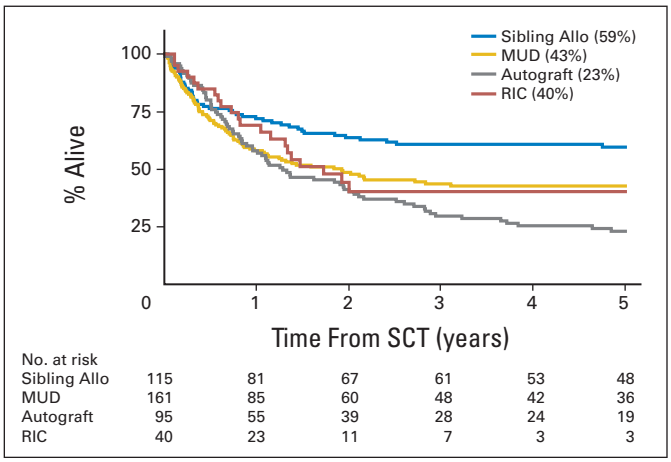

Fig 3. Survival from transplantation in second remission by type of transplant. Allo, allograft; MUD, matched unrelated donor; RIC, reduced-intensity allograft; SCT, stem-cell transplantation.

Within risk groups, with analyses censored at nonallogeneic transplant (Figs 4B to 4E), 35% of patients with good risk, 47% of patients with standard risk, 34% of patients with poor risk, and 53% of patients with unknown risk who received an allogeneic transplant survived compared with 44%, 15%, 0%, and 28%, respectively, for patients who did not receive any type of allograft. When the favorable group was split according to the type of abnormality, for patients with a t(8;21) mutation, the allograft survival was 29% versus 41% in patients who did not undergo transplantation, whereas for inv(16) patients, survival was 39% and 47%. There was no evidence of heterogeneity of effect by type of core binding factor leukemia ($P = .4$).

NPM1 *Status*

Because *NPM1* mutations are prognostically favorable, and patients are recommended not to receive an SCT in CR1, these cases were analyzed separately. In 256 *NPM1*-positive/*FLT3*-negative patients, the 5-year cumulative incidence of relapse was 39%; with a survival rate from relapse of 32%. The contribution of an allograft in CR2 to survival in the 43 patients who reached second remission was assessed in a Mantel-Byar analysis that compared the 15 patients who underwent transplantation with 28 patients who did not. There was a significant benefit of transplantation in this group (hazard ratio, 0.23; 95%

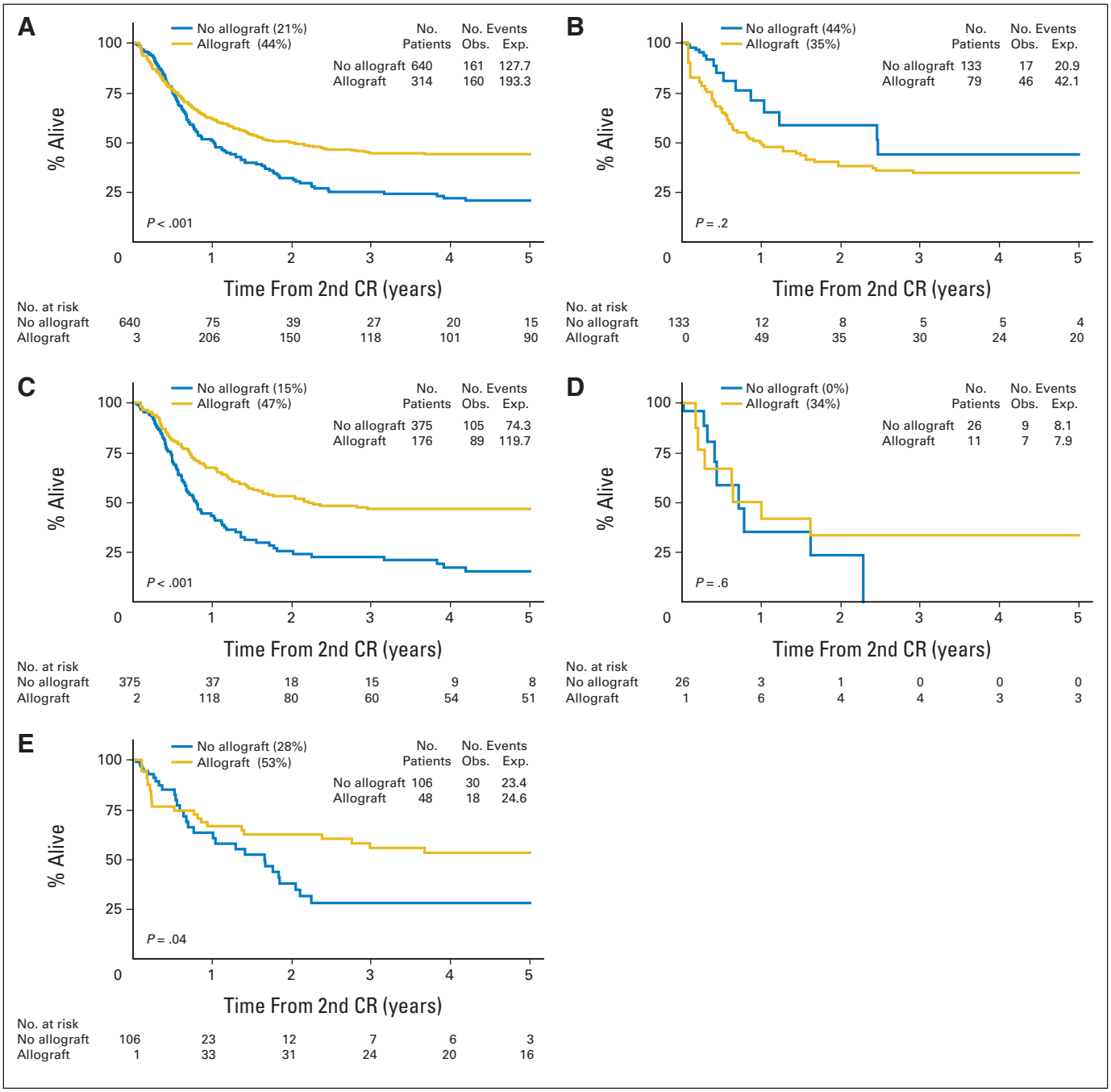

Fig 4. Mantel-Byar analysis of allogeneic transplant in second remission. (A) Survival from second complete remission (CR), allograft *v* not. (B) Survival from second CR, allograft *v* not favorable. (C) Survival from second CR, allograft *v* not intermediate. (D) Survival from second CR, allograft *v* not adverse. (E) Survival from second CR, allograft *v* not unknown risk. Analyses were censored at autograft. In the Mantel-Byar analysis, all patients started in the no-transplant group and transferred to the transplant group at the time of transplantation. Exp., expected number of events; Obs., observed number of events.

CI, 0.08 to 0.69; $P = .01$), with no significant evidence of heterogeneity of transplant benefit between these patients and those with other genotypes ($P = .1$; Fig 5).

DISCUSSION

The decision to offer a patient an SCT in CR1 is increasingly complex because new prognostic markers continue to emerge.[24-30] It is reasonable to conclude that if a patient has a chance of survival without relapse with chemotherapy alone of greater than 65%, then a transplant is unlikely to be beneficial. This chance of survival already accounts for core binding factor and *NPM1* subgroups and probably bi-allelic *CEBPα*. Even if the risk is higher, it could be balanced by the prospect of salvage treatment if relapse does occur to provide an equivalent overall survival to transplantation in CR1. In this study of a large number of patients did not undergo transplantation in CR1

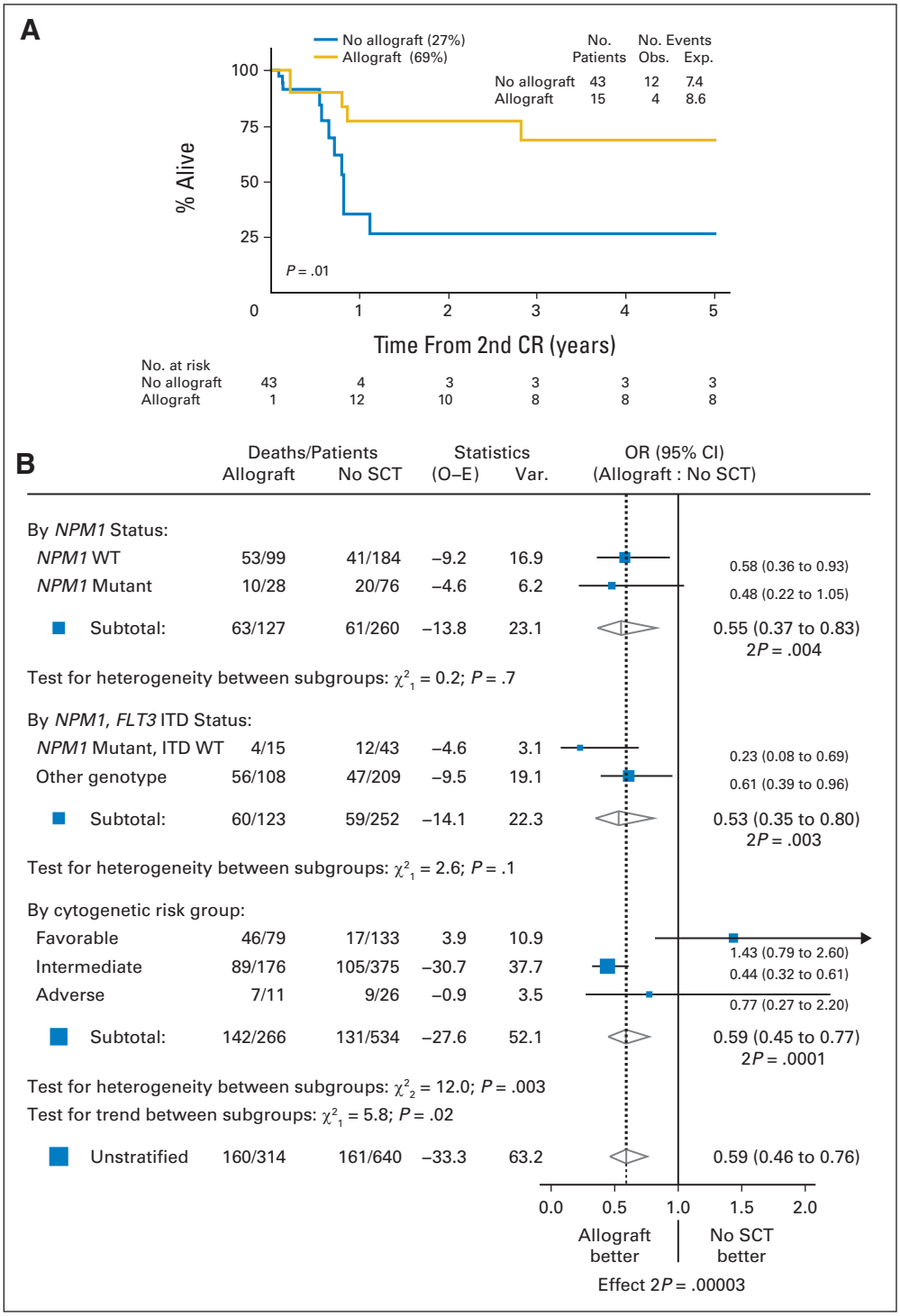

Fig 5. (A) Mantel-Byar analysis of allograft in second remission of patients with *NPM1* mutation, *FLT3*–internal tandem duplication (ITD) wild type (WT). In the Mantel-Byar analysis, all patients started in the no-transplant group and transferred to the transplant group at the time of transplantation. (B) Stratified analyses of allograft in second remission. CR, complete remission; Exp., expected events; Obs., observed events; O-E, observed minus expected; OR, odds ratio; SCT, stem-cell transplantation; Var., variance.

and relapsed, 19% of patients were alive after only receiving chemotherapy in CR1, whereas only 7% survived if they relapsed after transplant. In this study, we focused on 642 patients age 16 to 49 years who achieved a second remission of whom 433 underwent transplantation in CR2. These 433 patients accounted for 4.8% of all patients who entered these trials, and 11% of patients age 16 to 49 years. The data suggest the possibility of producing the same number of survivors overall by reserving transplantation for relapse, which would require many fewer transplants and avoid the transplant-associated morbidity and extra health-related interventions. This dilemma is particularly acute for patients with intermediate- risk disease. The decision requires the support of accurate information concerning the risk of relapse and, of relevance to this study, the possibility of successful salvage treatment of a patient when relapse happens.

It is generally accepted that, for patients with core binding factor AML or an isolated *NPM1* mutation, an allograft is not required in CR1. If a poor-risk patient relapses, the prognosis is poor (7% in this study), and thus, an allograft that can save approximately 30% of patients should be given in CR1. The priority is to adequately define poor-risk patients. The problem arises in the 60% of younger patients with intermediate-risk cytogenetics. The prospective trial data have produced an inconsistent message with respect to overall survival as opposed to relapse-free survival in this group, although overview analyses are generally interpreted as supporting the routine use of allograft in CR1.[9,10] However, these studies have some limitations, which we will discuss elsewhere. There is also the issue of the most cost effective use of a transplant. The question is as follows: how many transplants are required to cure a patient if a transplant is given to all patients in CR1 compared with a policy of reserving a transplant only for patients who experience failure of first-line chemotherapy? To answer this question, an accurate estimate of the prospect of salvage for each risk group is needed. Our data showed that 19% of all patients who did not undergo transplantation in CR1 were alive at 5 years from a relapse. The respective figures for favorable, intermediate, adverse, and unknown risks are 32%, 17%, 7%, and 23%. A basic assessment of the number of transplants needed per life saved can be obtained by performing landmark analyses, starting at the median time to transplant in CR1 (127 days in this study). Compared with a 66% survival in CR1 transplants, the landmark survival for patients who did not undergo a transplant is 72% for favorable-risk patients, which confirms a no-transplant policy. In intermediate-risk patients, the figures are 57% and 50%, respectively, with the former figure achieved with a 100% transplant rate, and the latter figure achieved with only a 20% transplant rate. These percentages equate to 11.4 transplants per life (80 transplants for seven additional lives). In adverse-risk patients, the fact that only 15 of 108 patients who relapse actually reach transplantation in second remission reduces the extent of any potential improvements to the cure rate from an allograft in CR2; together with 5-year survival rates of 34% versus 23%, these data support a policy of transplantation in CR1. For patients with an *NPM1*-positive/*FLT3*-negative mutation, again starting at the median time from CR to transplantation, a 5-year relapse-free survival of 54% translated to a 5-year survival from CR of 68% when the patients who received salvage treatment were considered.

The prognosis for patients who relapse after a CR1 transplant is poor (7% in our experience), which has established a previous transplant as an additional adverse factor for relapsing patients as reported by others.[31] It is clear that recipients of transplants in CR2 do better than those not undergoing transplantation in CR1 (42% *v* 16%, respectively), which may be partially because they are fit enough for a transplant. With the use of Mantel-Byar analysis, we attempted to determine the contribution of a transplant to salvage. The analysis confirmed the overall benefit, with the clearest evidence of a benefit coming from the intermediate-risk group. However, the data in the study did not support patients with favorable cytogenetics undergoing transplantation in CR2. Our findings remained consistent even when the date of recruitment of patients was allowed for.

The clear benefit for receipt of a transplant in CR2 for intermediate-risk patients raises an important question regarding timing. Importantly, patients who receive a transplant in CR1 are younger than patients who do not undergo transplantation and are fit enough to receive a transplant, and thus, our analyses likely overestimated the benefits of a transplant. However, in the nontransplanted group, only 13% of patients received a transplant in CR2, which could be limited by transplantation being deployed in CR1, and, that option having been used, not being available in CR2. This factor might also mean that more risky transplants were undertaken in CR2, which again might have led to an underestimation of the contribution that a CR2 transplant could make. These data, particularly for intermediate-risk disease, indicate that the same survival can be achieved with fewer transplants by reserving the receipt of an SCT to CR2. Another option is to go straight to transplantation without attempting reinduction therapy. Our limited experience of this approach is that it was not beneficial; however, it did result in a 9% survival rate and might be justified for patients in whom relapse is early, such as in patients with persistent residual disease and in whom the rapid delivery of a transplant is possible, although this requires validation. We are unable to say whether patients who received a transplant immediately on relapse did better than after a failed effort to reinduce remission. With the increasing incorporation of regular minimal residual disease monitoring, early relapses will be more frequently recognized, and the question is whether it is appropriate to go straight to transplantation or to attempt reinduction first. Ongoing studies incorporating minimal residual disease may help clarify this issue. Although the second remission rate in favorable risk is satisfactory (82% in this study), the rate in intermediate risk is suboptimal (35%). Improving this rate could improve salvage by enabling the transplant opportunity.

The decision to transplant is likely to remain complicated because relevant factors may well change. Several new prognostic factors will further stratify the relapse risk in intermediate patients; however, it cannot be assumed that adverse features are automatically improved by a transplant. The safety of transplantation may improve and the earlier detection of a relapse by molecular or immunophenotypic methods may enable a more effective intervention.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL REPORT

Post-Transplantation Lymphoproliferative Disorder After Kidney Transplantation: Report of a Nationwide French Registry and the Development of a New Prognostic Score

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ABSTRACT

Purpose
Post-transplantation lymphoproliferative disorder (PTLD) is associated with significant mortality in kidney transplant recipients. We conducted a prospective survey of the occurrence of PTLD in a French nationwide population of adult kidney recipients over 10 years.

Patients and Methods
A French registry was established to cover a nationwide population of transplant recipients and prospectively enroll all adult kidney recipients who developed PTLD between January 1, 1998, and December 31, 2007. Five hundred patient cases of PTLD were referred to the French registry. The prognostic factors for PTLD were investigated using Kaplan-Meier and Cox analyses.

Results
Patients with PTLD had a 5-year survival rate of 53% and 10-year survival rate of 45%. Multivariable analyses revealed that age > 55 years, serum creatinine level > 133 μmol/L, elevated lactate dehydrogenase levels, disseminated lymphoma, brain localization, invasion of serous membranes, monomorphic PTLD, and T-cell PTLD were independent prognostic indicators of poor survival. Considering five variables at diagnosis (age, serum creatinine, lactate dehydrogenase, PTLD localization, and histology), we constructed a prognostic score that classified patients with PTLD as being at low, moderate, high, or very high risk for death. The 10-year survival rate was 85% for low-, 80% for moderate-, 56% for high-, and 0% for very high–risk recipients.

Conclusion
This nationwide study highlights the prognostic factors for PTLD and enables the development of a new prognostic score. After validation in an independent cohort, the use of this score should allow treatment strategies to be better tailored to individual patients in the future.

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INTRODUCTION

Post-transplantation lymphoproliferative disorder (PTLD) is a rare but serious complication that occurs after solid organ transplantation.[1,2] PTLD has a specific pathophysiology, because it is often associated with Epstein-Barr virus (EBV) and is related to impaired immune surveillance. Moreover, PTLD has a predilection for extranodal sites, the brain, or the transplanted organ. Patients with PTLD receive different treatments than immunocompetent patients in terms of immunosuppression reduction, antiviral therapy, monotherapy with monoclonal antibodies, shorter immunochemotherapy, or graft removal. Nevertheless, no real consensus exists regarding treatment strategies in the setting of PTLD. Moreover, PTLD mortality remains high, with a 5-year overall survival (OS) rate ranging from 40% to 70% in most studies[1,3-7]; this highlights the need to investigate new prognostic factors for patients with PTLD. Because of the particularities of post-transplantation lymphoproliferation, a primary prognostic index, such as the International Prognostic Index (IPI),[8] which is used for immunocompetent patients, is not appropriate for the population undergoing transplantation[6,7,9] or for immunocompetent patients treated with immunochemotherapy.[10] Therefore, specific prognostic indices

have been proposed for the population undergoing transplantation,[6,7,9,11] which combine two or three of the following criteria: age > 60 years,[9] performance status ≥ 2,[6,7,9,12] presence of B symptoms,[12] elevated lactate dehydrogenase (LDH) levels,[9,12] hypoalbuminemia,[11] involvement of > one extranodal site,[7] involvement of the brain, bone marrow, or grafted organ,[6,11] and monomorphic disease.[6] However, these studies were either single-institution studies with a small number of patients[7,12] or studies combining kidney, pancreas, liver, heart, lung, and multiorgan transplant recipients, which contributed to significant heterogeneity among the groups.[6,9,11] In contrast, registry reports have included more patients, but information regarding recipient and PTLD characteristics has been limited.[3] For these reasons, we conducted a prospective survey of PTLD in a French nationwide population of adult kidney transplant recipients over 10 years. We constructed a new prognostic survival index to stratify patient risk.

PATIENTS AND METHODS

Patients

All new cases of PTLD diagnosed in kidney transplant recipients between January 1, 1998, and December 31, 2007, regardless of transplantation date, were prospectively enrolled from all adult kidney transplantation centers (n = 35) in France. Inclusion criteria were recipient age at the time of transplantation (> 18 years), kidney or simultaneous kidney and pancreas transplantation, biopsy-proven diagnosis of PTLD (or strong clinical suspicion when biopsy was not possible; n = 4), and occurrence of PTLD at any time after kidney transplantation; however, if graft failure occurred, only cases that occurred < 3 months after graft failure were included, because it is known that the risk of neoplasia decreases to that of the general population after cessation of immunosuppression.[13,14] Early lesions, polymorphic PTLD, monomorphic lymphomas (including Hodgkin diseases), and plasma cell neoplasms were included. Of the 601 patients referred to the French registry, 500 met the inclusion criteria (Appendix Fig A1, online only). Extensive data from donors and recipients were collected at the time of transplantation, at PTLD diagnosis, and once per year for up to 10 years after diagnosis. Immunosuppressive drugs were recorded at discharge after transplantation and at the time of PTLD diagnosis. Pathologists from each center performed the histological analyses. PTLD treatment was conducted in accordance with the general practice at each center. The French registry was approved by the Commission Nationale de l'Informatique et des Libertés (Paris, France; authorization No. 02.26). Informed consent was not obtained, because this was not a clinical trial but rather a prospective review of standard care.

Statistical Analysis

Survival data were collected from the date of PTLD diagnosis and analyzed on the reference date of July 1, 2010. Cox proportional hazards models were used to identify prognostic factors.[15,16] All variables associated with survival ($P \leq .20$; Appendix, online only) were entered into the multivariable Cox proportional hazards model. A backward stepwise selection procedure with a P value cutoff at .05 was then applied to identify a set of prognostic factors. Once this set was identified, two-by-two interactions between these variables were tested, and significant interactions were retained in the model. After the establishment of a multivariable model, a prognostic score was constructed by attributing a round score reflecting the relative weight of the regression coefficient to each variable in the model. Patients with CNS PTLD and T-cell PTLD were not included in this analysis, because their clinical presentation is different from that of other PTLDs, their prognosis is poor, and their management is specific.

Likelihood ratio (LR) statistics were computed for the multivariable proportional hazards models. A larger LR indicated a better fit to the data. However, LR value alone does not provide easy interpretation in terms of prognostic. For that purpose, the Gonen and Heller[17] concordance probability estimate (CPE) for the Cox model was used. Briefly, the CPE indicates the probability that in a random pair of observations, the patient with the smaller predicted risk will survive longer than the patient with the higher predicted risk. The CPE ranges between 0.5 and 1.0, with a value of 0.5 indicating a random prognostic and value of 1.0 indicating a perfect concordance between the ordering of risk prognostic and ordering of survival.

Table 1. Baseline Demographics and Clinical Characteristics of Patients With PTLD in French Registry

Characteristic	Missing		Patients	
	No.	%	No.	%
Recipient sex	0	0		
Female			167	33
Male			333	67
Age at transplantation, years	0	0		
18-32			95	19
32-46			145	30
46-60			189	38
> 60			71	14
Age at PTLD diagnosis, years	0	0		
18-32			27	5
32-46			121	24
46-60			178	36
> 60			174	35
Primary kidney disease	47	9		
Autosomal polycystic			70	15
Diabetic nephropathy			30	7
Glomerulonephritis			220	48
Tubulointerstitial chronic nephropathy			82	18
Vascular nephropathy			31	7
Other			20	4
Transplantation				
First	0	0	442	88
Subsequent			58	12
Donor status				
Deceased	0	0	484	97
Living			16	3
Serologic status				
Recipient				
CMV positive	46	9	261	57
EBV negative	127	25	50	13
HCV positive	83	17	38	9
HBV positive	52	10	25	6
Donor				
CMV positive	73	15	221	52
EBV positive	268	54	193	83
CMV donor positive, recipient negative	73	15	78	18
EBV donor positive, recipient negative	137	27	29	8
Immunosuppression at discharge	24	5		
Induction			398	84
Anti-CD3 monoclonal antibody			25	5
Antilymphocyte globulin			352	74
Anti-IL2 receptor antibody			37	8
Calcineurin inhibitors			454	95
Cyclosporine			378	79
Tacrolimus			76	16
Azathioprine			295	62
Mycophenolate mofetil			171	36
Proliferation signal inhibitors			12	2.5
Steroids			455	96

Abbreviations: CMV, cytomegalovirus; EBV, Epstein Barr virus; HCV, hepatitis C virus; HBV, hepatitis B virus; IL2, interleukin-2; PTLD, post-transplantation lymphoproliferative disorder.

Table 2. Presentation and Treatment of Patients With PTLD (N = 500)

Characteristic	Missing No.	Patients No.	Patients %
Early-onset PTLD, months	0		
< 12		72	14
< 18		97	19
Immunosuppression at diagnosis	32		
Calcineurin inhibitors		436	93
Cyclosporine		334	71
Tacrolimus		102	22
Azathioprine		156	33
Mycophenolate mofetil		201	43
Proliferation signal inhibitors		18	4
Steroids		310	66
Viral data			
CMV prophylaxis (after transplantation)	47	72	16
CMV infection (before PTLD)	47	114	25
Positive EBV viremia at PTLD diagnosis	247	167	66
Biologic data			
Dysglobulinemia	215	47	16
LDH > normal	190	144	46
Serum creatinine > 133 μmol/L	8	279	57
PTLD localization	11		
GI tract		120	24
Lymph nodes only		83	17
Brain		69	14
Graft		62	13
ENT		44	9
Skin and mucosa		31	6
Hematopoietic organs		23	5
Lung		21	4
Liver		20	4
Other		16	3
Disease status			
Single site		289	59
Disseminated		198	41
Histologic data			
B-cell PTLD	28	440	93
T-cell PTLD	28	29	6
Non–T-, non–B-cell PTLD	28	3	0.6
Polymorphic PTLD	63	117	27
Monomorphic PTLD	63	310	72
Hodgkin lymphoma	63	31	7
Myeloma	63	16	4
EBV-positive PTLD	138	249	69
Polyclonal PTLD	319	43	24
Monoclonal PTLD	319	137	76
Immunosuppression modification	46	421	93
Cyclosporine		334	
Cessation		169	51*
Reduction		103	31*
No change		49	15*
Unknown		13	
Tacrolimus		102	
Cessation		48	47†
Reduction		34	33†
No change		15	15†
Unknown		5	
Azathioprine		156	
Cessation		128	82‡
Reduction		4	3‡
No change		16	10‡
Unknown		9	
Mycophenolate mofetil		201	
Cessation		141	70§
Reduction		26	12§
No change		18	9§
Unknown		15	
CNI plus antimetabolite		326	
Modification of both		245	75‖
Modification of CNI only		23	7‖
Modification of antimetabolite only		30	9‖
No change		10	3‖
Steroid introduction		155	37
Steroid increase		64	20
PSI introduction		32	6
Antiviral therapy	22	92	19
Cytotoxic therapies	17		
Chemotherapy alone		141	29
Rituximab alone		81	17
Chemotherapy plus rituximab		169	35
Total chemotherapy		310	65
Total rituximab		250	52
Radiotherapy	20	59	12
Surgery	19	87	18
Transplantectomy		23	5

NOTE. For items with missing data, percentages are computed only with known patient cases.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein Barr virus; ENT, ear, nose, and throat; LDH, lactate dehydrogenase; PTLD, post-transplantation lymphoproliferative disorder.

*Percentage of the 334 patients treated with cyclosporine A at diagnosis.

†Percentage of the 102 patients treated with tacrolimus at diagnosis.

‡Percentage of the 156 patients treated with azathioprine at diagnosis.

§Percentage of the 201 patients treated with mycophenolate mofetil at diagnosis.

‖Percentage of the 326 patients treated with calcineurin inhibitor plus antimetabolite at diagnosis.

Missing data were handled through multiple imputations using the chained equations method[18] and considering the baseline mortality hazard. Sixty independent imputed data sets were generated and analyzed separately. Estimates of model parameters, survival rates, and concordance probabilities were then pooled over the 60 imputations according to Rubin's rules to provide point estimates and CIs for each parameter (Appendix, online only). The stability of the model selection procedure and a correction for overoptimism were performed using bootstrap resampling with 200 replications.

All tests were two sided, and P values $\leq .05$ were considered statistically significant. The means are given, followed by standard deviations (SDs), and the intervals provided are ranges. Analyses were performed using R statistical software, version 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic Features

Over the 10-year period, PTLD occurred in 167 women and 333 men who received kidney (n = 483) or simultaneous kidney and

pancreas (n = 17) transplants. Eighty-five patients (17%) had received immunosuppression treatment before transplantation (for primary kidney disease or previous transplantation). The year of transplantation ranged from 1967 to 2007. The demographic characteristics of the study participants are summarized in Table 1. The mean (± SD) recipient age was 53 ± 12 years at PTLD diagnosis (range, 22 to 79 years). One hundred three patients (21%) experienced an acute rejection episode before PTLD diagnosis. The mean delay for PTLD occurrence was 95 ± 73 months, with a median of 89 months (range, 1 to 397 months). Early-onset PTLD (diagnosed within the first 12 months after transplantation) occurred in 14% of patients. The characteristics of patients at the time of PTLD diagnosis and clinical and histological presentation of PTLD are summarized in Table 2. At the time of PTLD diagnosis, the mean serum creatinine level was 165 ± 95 μmol/L (46 μmol/L to dialysis). Of note, 13% of the PTLDs involved the kidney allograft itself, and 14% developed in the brain. The GI tract was the most common localization (24% of patient cases). The management of patients is summarized in Table 2. Briefly, rituximab was used in 250 patient cases, and chemotherapy was used in 310; 169 patients received both therapies. Acute rejection occurred in 24 patients (5%) after PTLD. A total of 251 patients died; of these deaths, 137 (55%) resulted from PTLD progression, 47 (18%) from complications of PTLD treatment, 22 (8%) from cardiovascular disease, 42 (16%) from other causes, and three (0.6%) from unknown reasons. Ninety-nine patients (20%) returned to dialysis, 18 (27%) of whom underwent retransplantation, with a mean delay of 73 ± 25 months after PTLD diagnosis (range, 33 to 123 months).

Patient Survival and Prognostic Factors

The median follow-up was 7.5 years (fifth percentile, 2.8; 95th percentile, 12.1). The 1-, 3-, 5-, and 10-year OS rates were 68%, 58%, 53%, and 45%, respectively (Fig 1). The median survival time was 6.6 years. Patient survival considering only deaths related to PTLD is provided in Appendix Figure A2 (online only).

Univariate analysis (Table 3) showed that induction therapy with anti–interleukin-2 (IL2) receptor antibodies, early-onset PTLD, and decrease in immunosuppression were significantly associated with better survival. The following factors were associated with poor OS: age > 55 years at PTLD diagnosis, serum creatinine level > 133 μmol/L at diagnosis, elevated LDH level, disseminated PTLD, CNS localization, spread of PTLD over the serous membranes, monomorphic PTLD, and T-cell PTLD. The results from the imputed data sets were the same (Table 3). Survival according to localization is shown in Appendix Figure A3 (online only). In the multivariable analysis (Table 4), the following variables were associated with a lower OS rate: age > 55 years at diagnosis, serum creatinine level > 133 μmol/L at diagnosis, elevated LDH levels, disseminated PTLD, CNS PTLD, serous membrane invasion, T-cell PTLD, and monomorphic PTLD. In contrast, induction therapy with anti-IL2 receptor antibodies was significantly associated with better survival.

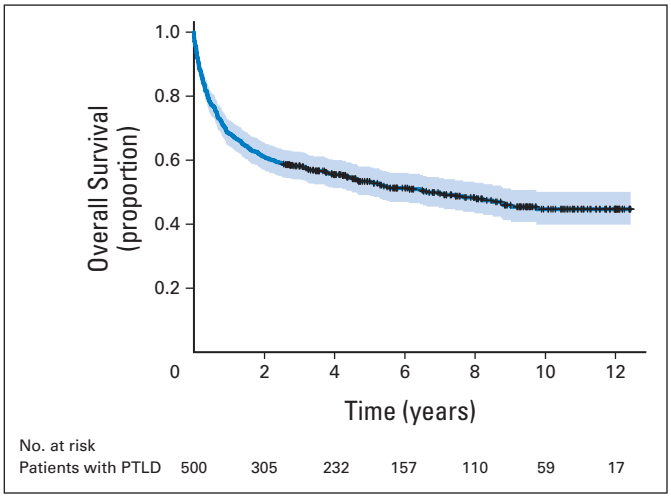

Fig 1. Overall survival of patients with post-transplantation lymphoproliferative disorder (PTLD). Shaded area represents pointwise 95% CI.

Prognostic Score

A prognostic score was constructed using the following variables determined at diagnosis: age > 55 years, serum creatinine level > 133 μmol/L, elevated LDH, disseminated PTLD, and monomorphic histology. Serous membrane invasion was not retained in the score because of its rarity; additionally, anti-IL2 receptor antibody induction was not considered, because the score was based on variables collected at the time of PTLD diagnosis. On the basis of the regression coefficients and because of the significant interaction between age and serum creatinine level (Appendix Table A1, online only), the presence of elevated LDH, disseminated PTLD, and monomorphic PTLD was given one point, and the presence of serum creatinine level > 133 μmol/L was given two points if the patient was > 55 years of age. The final score ranged from 0 to 5. Using this score, patients were classified into the following categories: very high risk (score of 4 or 5), high risk (score of 2 or 3), moderate risk (score of 1), and low risk (score of 0). In the original data set, 1-, 5-, and 10-year OS rates were 100%, 92%, and 85%, respectively, for low-risk patients; 89%, 83%, and 80%, respectively, for moderate-risk patients; 74%, 59%, and 56%, respectively, for high-risk patients; finally, and 52%, 35%, and 0%, respectively, for very high–risk patients (Fig 2A; Appendix Table A2, online only). The median survival time was 8 months for very high–risk recipients and 9 years for high-risk recipients; it was not reached for moderate- or low-risk patients. When applied to the entire population (including patients with T-cell PTLD or CNS PTLD), the score maintained its discriminative ability (Fig 2B). Additionally, an analysis based on the multiple imputation of missing data confirmed that the prognostic index was able to accurately discriminate between different risk levels (Figs 2C and 2D; Appendix Table A2, online only). Using imputed data, we showed that PTLD-specific mortality was low in patients with a score of 0 (3.3%; 95% CI, 0.4% to 9.5%), intermediate in patients with a score of 1 (18.7%; 95% CI, 10.7% to 28.4%), high in patients with a score of 2 or 3 (35.8%; 95% CI, 29% to 42.6%), and very high in patients with a score of 4 or 5 (60.8%; 95% CI, 40.5% to 76.1%; Appendix Figs A4A and A4B, online only).

DISCUSSION

This study indicates that the prognosis of kidney transplant recipients with PTLD is still poor, with a 5-year survival rate of 53% and 10-year survival rate of only 45%. These survival rates are slightly better than those reported in the Collaborative Transplant Study, in which the 5-year mortality rate in kidney transplant recipients was approximately 40%[1]; however, they are lower than those reported in the US

Table 3. Univariable Analysis of Patient OS: Original Data and Imputed Data Sets

Variable	Original Data Set			Pooled Over Imputed Data Sets		
	HR	95% CI	*P*	HR	95% CI	*P*
Female sex	0.88	0.67 to 1.15	.36	0.88	0.67 to 1.15	.36
Age at diagnosis > 55 years	1.85	1.44 to 2.39	< .001	1.85	1.44 to 2.39	< .001
Primary kidney disease (*v* glomerulonephritis)						
TICN	0.65	0.28 to 1.47	.30	0.68	0.31 to 1.52	.35
APKD	1.27	0.87 to 1.84	.21	1.25	0.87 to 1.79	.22
Vascular nephropathy	1.14	0.79 to 1.64	.47	1.15	0.80 to 1.64	.45
Diabetic nephropathy	1.10	0.63 to 1.92	.74	1.16	0.67 to 1.98	.60
Other	1.50	0.92 to 2.45	.10	1.53	0.94 to 2.49	.085
CMV-positive recipient	1.26	0.96 to 1.65	.10	1.20	0.92 to 1.56	.19
CMV-positive donor	1.25	0.95 to 1.65	.10	1.27	0.97 to 1.65	.082
EBV-positive recipient	1.33	0.82 to 2.14	.24	1.14	0.73 to 1.78	.55
EBV-positive donor	1.26	0.75 to 2.12	.38	0.94	0.67 to 1.32	.72
HCV-positive recipient	1.31	0.84 to 2.04	.23	1.35	0.89 to 2.04	.15
Immunosuppressive therapy before transplant	0.82	0.59 to 1.16	.26	0.82	0.59 to 1.16	.26
Occurrence of CMV disease	1.28	0.89 to 1.84	.18	1.28	0.89 to 1.84	.18
Early-onset PTLD ≤ 12 months	0.53	0.35 to 0.80	.003	0.53	0.35 to 0.80	.003
Antilymphocyte globulin	1.12	0.83 to 1.51	.44	1.10	0.82 to 1.48	.51
Anti-CD3 monoclonal antibody	0.72	0.38 to 1.35	.30	0.74	0.40 to 1.38	.34
Anti-IL2 receptor antibody	0.42	0.22 to 0.83	.01	0.43	0.22 to 0.83	.01
Serum creatinine > 133 μmol/L*	1.41	1.09 to 1.83	.009	1.42	1.10 to 1.84	.008
Elevated LDH*	2.04	1.46 to 2.84	< .001	1.91	1.42 to 2.57	< .001
Disseminated PTLD	1.57	1.22 to 2.03	< .001	1.57	1.22 to 2.02	< .001
PTLD localization (*v* other localizations)						
Graft	0.72	0.46 to 1.15	.17	0.73	0.46 to 1.16	.18
Lymph nodes	0.95	0.64 to 1.40	.78	0.94	0.63 to 1.39	.75
GI tract	1.28	0.92 to 1.79	.15	1.29	0.92 to 1.80	.14
CNS	1.75	1.21 to 2.53	.003	1.77	1.22 to 2.56	.002
Bone marrow invasion	1.18	0.72 to 1.94	.50	1.17	0.71 to 1.92	.55
Serous membrane invasion	3.58	2.20 to 5.80	< .001	3.50	2.10 to 5.81	< .001
T-cell PTLD	1.94	1.24 to 3.04	.004	1.92	1.24 to 2.97	.004
Monomorphic PTLD	1.64	1.18 to 2.28	.003	1.62	1.18 to 2.22	.003
Immunosuppression decrease†	0.51	0.33 to 0.80	.004		–	–

Abbreviations: APKD, autosomic polycystic kidney disease; CMV, cytomegalovirus; EBV, Epstein Barr virus; HCV, hepatitis C virus; HR, hazard ratio; IL2, interleukin-2; LDH, lactate dehydrogenase; OS, overall survival; PTLD, post transplantation lymphoproliferative disease; TICN, tubulointerstitial chronic nephropathy.

*At diagnosis.

†Not imputed because of complex missing data mechanism (missing data regarding some immunosuppressive treatments at diagnosis and data regarding possible tapering); analysis included 440 patients.

registry, in which the 5-year survival rate was 64%.[19] This finding highlights the need to optimize the management of PTLD in transplant recipients by intensifying procedures in some cases but avoiding treatment toxicity in other cases because of the fragility of patients undergoing transplantation.

Age > 55 years at PTLD diagnosis, late-onset PTLD, elevated LDH and serum creatinine levels, widespread PTLD, CNS localization, T-cell lymphoma, and monomorphic histology were associated with poor survival, whereas a decrease in immunosuppression was associated with a better prognosis. Age at diagnosis is known to be an important prognostic factor; however, the adopted age cutoff for the stratification of patient risk is 60 years based on the IPI.[8] In our series of transplant recipients, 55 years of age was shown to be a better threshold. Older transplant recipients often have comorbidities and are exposed to infectious complications, which may explain why the age threshold is lower in this population than in immunocompetent patients.

Additional prognostic parameters reveal the burden of the tumor: LDH level, dissemination of PTLD, and localization to serous membranes. Dissemination of PTLD, stage of disease or localization at > one extranodal site, and increased LDH level have already been proposed as prognostic factors.[7,9,12,20] When used as a continuous variable, LDH level was associated with mortality in 60 patients in a study by Choquet et al.[9] LDH level was also associated with mortality in a Mayo Clinic series when the level was above normal.[6,12] Involvement of the CNS has been found to be associated with progression in other studies,[21,22] with an 88% mortality rate observed within 6 months in the US cohort.[11,23]

Prognostic factors are related to lymphoproliferation histopathology. T-cell lymphomas were associated with poor survival in our study; only 20% of these patients were alive after 10 years. T-cell lymphoma prognosis is poor because the tumor is unresponsive to immunosuppression reduction and rituximab, and it is usually refractory to chemotherapy.[7,24] Similar to the findings of the Mayo Clinic study,[6] monomorphic histology was associated with a worse prognosis in our study. This finding differs from those reported in the other studies, likely because the sample sizes were too small in these studies.[7,9] However, it is well known that polymorphic tumors represent

Table 4. Multivariable Analysis of Patient OS: Analysis of Imputed Data Sets

Variable	AHR	95% CI	*P*
Age at diagnosis > 55 years	2.18	1.68 to 2.84	< .001
Induction with anti-IL2 receptor antibody	0.44	0.22 to 0.86	.016
Serum creatinine > 133 μmol/L*	1.40	1.07 to 1.83	.013
Elevated LDH*	1.78	1.30 to 2.45	< .001
Disseminated PTLD	1.54	1.14 to 2.07	.005
CNS PTLD	2.65	1.85 to 3.79	< .001
Serous membrane invasion	3.19	1.83 to 5.54	< .001
T-cell PTLD	1.87	1.16 to 3.02	.011
Monomorphic PTLD	1.42	1.02 to 1.98	.037
LR		128.7	
CPE		0.690	
95% CI		0.660 to 0.719	

Abbreviations: AHR, adjusted hazard ratio; CPE, concordance probability estimate; IL2, interleukin-2; LDH, lactate dehydrogenase; LR, likelihood ratio test statistic; OS, overall survival; PTLD, post-transplantation lymphoproliferative disease.
*At diagnosis.

an earlier stage of lymphocyte proliferation and respond better to a reduction of immunosuppression.[25,26]

Prior studies have found that EBV tumor negativity and late PTLD were associated with poor survival.[27] In our study, early-onset PTLD showed a better prognosis in univariate analyses, but this relationship was no longer significant in multivariable analyses. EBV tumor negativity was not correlated with outcome in our cohort; however, EBV tumor staining was missing in one quarter of our sample.

Graft organ involvement was found to be predictive of mortality only in studies including lung or heart and lung transplant recipients,[6] because the prognosis of lung lymphoproliferation is poor in this population. In our study, kidney allograft involvement was associated with better prognosis, but this association did not persist after adjustment for confounders.

Finally, we found that serum creatinine level was associated with patient survival, which is in accordance with studies in both the general population and patients undergoing kidney transplantation, in whom renal insufficiency was associated with a higher mortality rate.[28] However, this association has not been previously reported in patients with PTLD. This may be the result of different factors, including inadequate dose of chemotherapy drugs, increased susceptibility to therapy toxicity, or increased incidence of cardiovascular morbidity in patients with kidney failure.

Using the strongest prognostic factors established by multivariable analyses, we constructed a specific PTLD prognostic index that stratifies patients according to their risk of death. The results from our

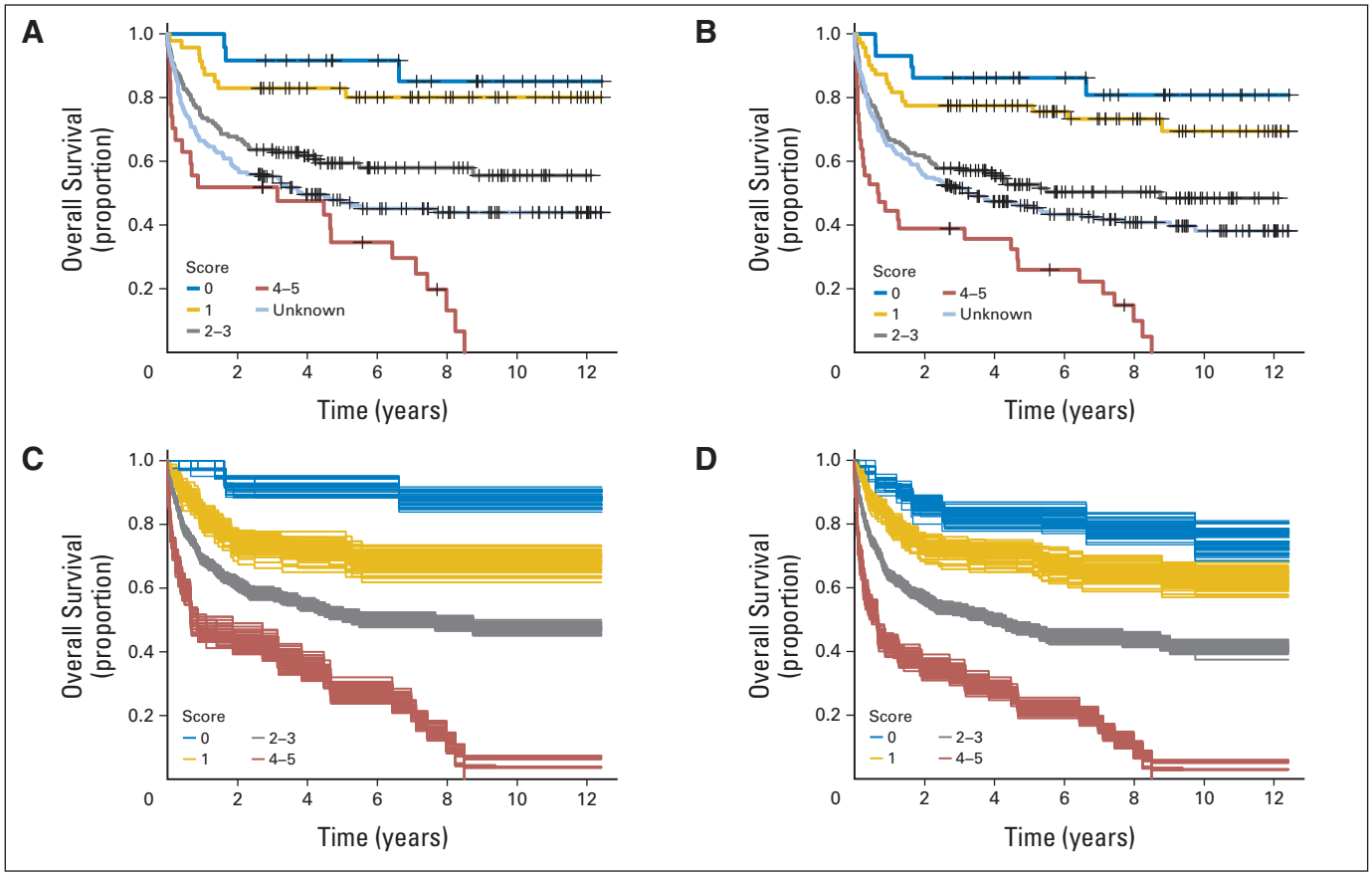

Fig 2. Overall survival rates according to score. (A) Original data set without patients with T-cell post-transplantation lymphoproliferative disorder (PTLD) or CNS PTLD (score of 0, n = 24; score of 1, n = 47; scores of 2 and 3, n = 121; scores of 4 and 5, n = 27; unknown score, n = 161). (B) Original data set including patients with T-cell or CNS PTLD (score of 0, n = 29; score of 1, n = 71; scores of 2 and 3, n = 147; scores of 4 and 5, n = 36; unknown score, n = 217). (C) Imputed data sets without patients with T-cell or CNS PTLD (score of 0, average n = 38; score of 1, average n = 92; scores of 2 and 3, average n = 216; scores of 4 and 5, average n = 53). (D) Imputed data sets including patients with T-cell or CNS PTLD (score of 0, average n = 52; score of 1, average n = 125; scores of 2 and 3, average n = 256; scores of 4 and 5, average n = 67).

study demonstrate that patients with a score of 4 to 5 had a 5-year survival rate of 35%, whereas patients with a score of 0 had a 5-year survival rate of 92%. In the latter group, care must be taken not to add excessive toxicity in the treatment procedures. In contrast, a score of ≥ 4 mandates prompt aggressive therapeutic strategies. Previous studies have shown that the IPI,[8] which is widely used for immunocompetent patients, is not suitable for patients undergoing transplantation[6,7,9]; this is in part because the lymphoma is located in lymph nodes in the majority of immunocompetent patients with lymphoma, whereas PTLD is typically extranodal. Some authors have proposed a specific prognostic index for transplant recipients based on several variables, including age, performance status, LDH level, albuminemia, dissemination of disease, monomorphic histology, and presence of B symptoms.[6,7,9,11,12] Some specific scores developed for transplant recipients with PTLD performed better than the IPI regarding the separation of the survival outcomes of patients.[6,7,9] Nevertheless, these scores were constructed either with a small number of kidney transplant recipients,[7,9,12] leading to an underestimation of the role of several variables because of a lack of power, or with a solid organ transplantation population,[6,11] leading to a combination of variables with opposite effects, depending on the type of grafted organ (eg, graft involvement or PTLD delay). The key features of our index are the large number of included patients and restriction to kidney transplant recipients. Moreover, the consideration of creatinine level in our score enhances the prognosis evaluation in the population of kidney transplant recipients. The absence of data on performance status in patient records is an obvious limitation of this study. Care of transplant recipients and declaration of PTLD cases to the registry were typically performed by nephrology centers, where physicians are not familiar with this evaluation. Given that performance status was missing, we were not able to assess the IPI in our patients or compare the IPI with our PTLD-specific index or other PTLD-specific indices. Nevertheless, we believe that the inclusion of our five criteria in the PTLD-specific score enabled us to correctly describe patient survival with good discrimination among risk groups.

In conclusion, PTLD after solid organ transplantation remains a challenging clinical issue. The strengths of our study include the long recruitment period and large sample size, which allowed us to obtain strong results regarding PTLD prognostication. Importantly, our prognostic index is specifically tailored for kidney transplant recipients. After validation in a homogeneous replication cohort, our score may set the stage for the development of individualized treatment recommendations tailored to a patient's risk profile.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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ORIGINAL REPORT

T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

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ABSTRACT

Purpose
T-cell–replete grafts from haploidentical donors using post-transplantation cyclophosphamide may represent a solution for patients who require allogeneic hematopoietic cell transplantation (alloHCT) but lack a conventional donor. We compared outcomes of alloHCT using haploidentical donors with those of transplantation using conventional HLA-matched sibling donors (MRDs) and HLA-matched unrelated donors (MUDs).

Patients and Methods
Outcomes of 271 consecutive patients undergoing T-cell–replete first alloHCT for hematologic malignancies performed contemporaneously at a single center (53 using haploidentical donors; 117, MRDs; 101, MUDs) were compared. Overall and disease-free survival (DFS) were adjusted for effects of significant patient-, disease-, and transplantation-related covariates using a stratified Cox model.

Results
Patient characteristics were similar between the three donor groups. For patients undergoing MRD, MUD, and haploidentical transplantation, 24-month cumulative incidences of nonrelapse mortality were 13%, 16%, and 7% and of relapse were 34%, 34%, and 33%, respectively (*P* not significant [NS]). Cumulative incidences of grades 3 to 4 acute graft-versus-host disease (GVHD) at 6 months were 8%, 11%, and 11%, respectively (*P* NS); extensive chronic GVHD occurred in 54%, 54%, and 38% of patients, respectively ($P < .05$ for those undergoing haploidentical donor *v* MRD or MUD transplantation). Adjusted 24-month probabilities of survival were 76%, 67%, and 64% and of DFS were 53%, 52%, and 60%, respectively; these were not significantly different among the three donor groups.

Conclusion
Haploidentical transplantation performed using T-cell–replete grafts and post-transplantation cyclophosphamide achieves outcomes equivalent to those of contemporaneous transplantation performed using MRDs and MUDs. Such transplantation represents a valid alternative for patients who lack a conventional donor.

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INTRODUCTION

For patients with hematologic malignancies who may benefit from allogeneic hematopoietic cell transplantation (alloHCT), HLA-matched siblings (MRDs) or HLA-matched unrelated donors (MUDs) are considered optimal donors. However, many patients, particularly those from ethnic minority and mixed-race backgrounds, lack such donors. Almost all patients have an available related donor with whom they share a single HLA haplotype (ie, haploidentical donor). Early attempts to use T-cell–replete grafts from haploidentical donors using conventional preparative regimens were associated with unacceptable rates of graft-versus-host disease (GVHD) and graft rejection.[1] Prior attempts to overcome these obstacles to haploidentical alloHCT entailed stringent ex vivo T-cell depletion of the graft, often combined with intense preparative regimens. Although such transplantation has been

demonstrated as feasible, it is associated with slow immune reconstitution and a high rate of nonrelapse mortality (NRM).[2,3] Recently, an alternative approach to haploidentical alloHCT was developed, which uses T-cell–replete bone marrow grafts in combination with post-transplantation cyclophosphamide to prevent GVHD and graft rejection.[4] This approach has demonstrated promising results, including acceptable rates of NRM and severe GVHD in single- and multi-institution phase II trials.[5-7] However, the results from such haploidentical alloHCT have not formally been compared with those of alloHCT using MRDs and MUDs. In particular, it remains unclear whether the greater level of HLA mismatch associated with such haploidentical transplantation results in higher NRM and poorer survival when compared with transplantation performed using optimally HLA-matched conventional donors. To address this question, we compared outcomes of consecutive patients undergoing T-cell–replete haploidentical alloHCT performed at our center with all contemporaneous T-cell–replete alloHCT using MRDs and MUDs.

PATIENTS AND METHODS

Patients

All consecutive patients undergoing first alloHCT for a hematologic malignancy between February 2005 and October 2010 at our center using haploidentical donors (n = 53), MRDs (n = 117), or MUDs (n = 101) were included in this retrospective comparison. A patient underwent transplantation using a haploidentical donor at our center if there was no available MRD or MUD or if a suitable MRD or MUD was unavailable within the timeframe appropriate for the patient's malignancy and clinical circumstances. The time period was chosen to ensure that all living patients had a minimum follow-up of 1 year at the time of analysis. Median follow-up for surviving patients was 36 months (range, 12 to 79.5 months) at the time of analysis. Regimens were classified as myeloablative transplantation versus reduced-intensity conditioning transplantation (RICT)/nonmyeloablative stem-cell transplantation (NST) based on previously defined guidelines.[8,9] For purposes of statistical analysis, RICT regimens were combined with NST regimens and compared with myeloablative conditioning. MRD and MUD transplantations were performed using a variety of preparative regimens (RICT/NST regimens used for MRD and MUD transplantations are listed in Appendix Table A1, online only). No graft was subjected to ex vivo T-cell depletion. Supportive-care algorithms were identical for patients in the three donor groups. All patients were similarly managed in the outpatient setting, with admission reserved for complications or symptoms that could not be adequately managed without inpatient admission.

Haploidentical Donor Transplantation Regimens

Patients underwent alloHCT using haploidentical donors with one of two regimens. Thirty-five patients received a nonmyeloablative regimen that has previously been described,[5-7] consisting of fludarabine 30 mg/m^2 intravenously (IV) once per day on days −6 to −2; total-body irradiation (TBI) 2 Gy on day −1, and cyclophosphamide 14.5 mg/kg IV once per day on days −6 and −5 and 50 mg/kg once per day on days 3 and 4 with a bone marrow graft. Eighteen patients were treated on an institutionally developed myeloablative protocol using fludarabine 25 mg/m^2 IV once per day on days −6 to −2, busulfan 110 to 130 mg/m^2 IV once per day on days −7 to −4, and cyclophosphamide 14.5 mg/kg IV once per day on days −3 and −2 and 50 mg/kg once per day on days 3 and 4, with granulocyte colony-stimulating factor–mobilized peripheral blood stem cells (PBSCs; target CD34+ cell count, 5×10^6/kg) as the graft. No pharmacokinetic adjustment of busulfan dose was performed. All patients received tacrolimus from days 5 to 180, with a target level of 5 to 15 ng/mL, and mycophenolate mofetil (maximum dose, 3 g per day in divided doses) on days 5 to 35. Filgrastim 5 μg/kg was administered from day 5 until neutrophil recovery. Human investigations were performed after approval by the local human investigations committee and in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

End Points

Primary outcomes analyzed were overall survival, disease-free survival (DFS; survival without evidence of active malignancy after transplantation), relapse of malignancy, NRM, acute GVHD, and chronic GVHD. Acute GVHD was classified as clinically significant (grades 2 to 4) or severe (grades 3 to 4). Because of the possibility of delayed onset of clinical acute GVHD after transplantation performed using RICT/NST regimens, cumulative incidence of acute GVHD was assessed at 6 months after transplantation. Chronic GVHD was classified as limited or extensive and also classified as mild, moderate, or severe by National Institutes of Health consensus criteria.[10] Acute and chronic GVHD were evaluated and graded by a single practitioner within the program. NRM and relapse were treated as competing risks. Graft failure was described as absolute neutrophil count $< 0.5 \times 10^9$/L in the presence of poor donor myeloid chimerism (CD33+ cells < 5% donor).

Statistical Methods

Comparisons of patient characteristics between transplantation groups were performed using the Kruskal-Wallis test for age and χ^2 test for categorical data. Cumulative incidences of NRM, relapse, acute GVHD, and chronic GVHD were computed to account for presence of competing risks.[11] Variables considered in multivariate analyses of overall survival and DFS included age, sex, diagnosis, regimen type (myeloablative *v* NST/RICT), graft type (PBSC *v* marrow), Karnofsky performance score, Center for International Blood and Marrow Transplant Research (CIBMTR) disease risk category, and Hematopoietic Cell Transplantation–Specific Comorbidity Index score.[12] Effects of these variables were assessed in Cox models with transplantation groups as strata to allow the baseline hazard functions to vary by type of transplantation. A backward stepwise selection procedure was performed on both overall survival and DFS, with a significance level of 0.1. On the basis of the significant variables, time-dependent variables were created and temporarily included in Cox models to test the proportional hazards assumption. Interactions between the main effects were examined at the same significance level of 0.1, but no interaction effect was significant. The adjusted overall survival and DFS of different types of transplantation were computed as average survival estimates of the pooled sample, weighted by the proportions of the significant variables in the Cox models.[13,14] Postrelapse/progression survival (PRS) was evaluated based on survival times of patients who experienced relapse or progression of their malignancy; the time origin was date of relapse. The follow-up time for PRS was obtained by subtracting the time to relapse from the total follow-up time. PRS can be confounded by the problem of dependent censoring. Specifically, the length of follow-up after relapse depends on the time to relapse and can distort the accurate measurement of PRS. To correct for this phenomenon and adjust for dependent censoring, the inverse probability censoring weighted method[15] was used for estimation of PRS. Outcome comparisons between transplantation using haploidentical donors and MRDs as well as between haploidentical donors and MUDs were of primary study interest. Significance was assessed using the Wald test and was conducted on NRM, relapse, acute GVHD, chronic GVHD, adjusted overall survival, adjusted DFS, and PRS at the fixed time points.[11] In one outcome, a comparison associated with $P < .05$ was identified as significant based on Bonferroni adjustment to control the overall type I error rate at a level of 0.1.

Global tests were also conducted to compare survival outcomes between transplantation using haploidentical donors and MRDs as well as between haploidentical donors and MUDs over the entire study period. 95% confidence bands for differences in adjusted overall survival and DFS between transplantation using haploidentical donors and MRDs and between those using haploidentical donors and MUDs were constructed through simulation.[13,15,16] Adjusted overall survival and DFS were not considered significantly different between two types of transplantation if the horizontal zero line was contained within the confidence band. Gray's tests[17] were conducted to compare cumulative incidences of a competing-risk end point between transplantation using haploidentical donors and MRDs and between transplantation using haploidentical donors and MUDs. Gray's global tests were evaluated, respectively, on NRM, relapse, acute GVHD, and chronic GVHD.

RESULTS

Patient Characteristics

Characteristics of patients studied in this analysis are listed in Table 1. The groups were well matched, except that patients undergoing alloHCT using haploidentical donors were significantly more likely to receive bone marrow grafts and an RICT/NST regimen. Patients undergoing alloHCT using haploidentical donors were mismatched at a median of five of 10 HLA-A, -B, -C, -DRB1, and -DQB1 loci by high-resolution molecular typing (range, two to five). MRDs were HLA identical to recipients in 114 patient cases (97.5%) and mismatched at a single HLA locus (nine of 10 HLA-A, -B, -C, -DRB1, and -DQB1 loci match) in three patients (2.5%; HLA-A locus mismatch in all patient cases). MUDs were matched at 10 of 10 loci in 87 patients (86%) and nine of 10 loci in 14 patients (14%; mismatched locus: HLA-A, n = 3; HLA-B, n = 2; HLA-C, n = 4; HLA-DQ, n = 5). Donor-cell engraftment occurred in 114 transplantations using MRDs (97.5%), 99 using MUDs (98%) and 52 using haploidentical donors (98%).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	MRD (n = 117) No.	%	MUD (n = 101) No.	%	Haploidentical (n = 53) No.	%	*P*
Median age, years	50		51		46		
Sex							.286
Male	75	64	55	54	29	55	
Female	42	36	46	46	24	45	
KPS							.319
< 90	32	27	35	35	20	38	
≥ 90	85	73	66	65	33	62	
Prior autotransplantation							.647
Yes	19	16	12	12	9	17	
No	98	84	89	88	44	83	
HCTCI score							.807
0 or 1	44	64	69	68	30	68	
≥ 2	25	36	32	32	14	32	
CIBMTR risk							.593
Low	37	32	27	27	18	34	
Intermediate	16	13	21	21	10	19	
High	64	55	53	52	25	47	
Diagnosis							.253
ALL	12	10	19	19	10	19	
AML	37	32	37	36	17	32	
NHL	25	21	14	14	5	9	
HL	7	6	4	4	6	11	
CLL	3	2.5	5	5	7	13	
CML/MPS	11	9.5	11	11	4	7.5	
MDS	11	9.5	7	7	4	7.5	
MM	9	7.5	4	4	0	0	
Other	2	1.5	0	0	0	0	
Regimen type							< .001
Myeloablative	70	60	47	46	18	34	
RICT/NST	47	40	54	54	35	66	
Cell source							< .001
PBSC	108	92	95	94	21	40	
BM	7	6	6	6	32	60	
PB + BM	2	2	0	0	0	0	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CIBMTR, Center for International Blood and Marrow Transplant Research; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HCTCI, Hematopoietic Cell Transplantation–Specific Comorbidity Index; HL, Hodgkin lymphoma; KPS, Karnofsky performance score; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPS, myeloproliferative syndrome; MRD, matched related donor; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma; NST, nonmyeloablative stem-cell transplantation; PB, peripheral blood; PBSC, peripheral blood stem cell; RICT, reduced-intensity conditioning transplantation.

GVHD

Rates of acute GVHD did not significantly differ by donor type (Figs 1A, 1B). Cumulative incidences of grades 2 to 4 acute GVHD at 6 months were 27%, 39%, and 30% for patients undergoing transplantation using MRDs, MUDs, and haploidentical donors, respectively; cumulative incidence rates for severe (grades 3 to 4) acute GVHD at 6 months were 8%, 11%, and 11%, respectively.

Chronic GVHD was significantly less frequent and less severe in patients undergoing transplantation using haploidentical donors than those undergoing transplantation using conventional donors on point-wise comparison (Figs 1C, 1D). Cumulative incidences of clinically extensive chronic GVHD at 24 months were 54%, 54%, and 38% for patients undergoing transplantation using MRDs, MUDs, and haploidentical donors, respectively ($P < .05$ for those undergoing haploidentical donor *v* MRD and MUD transplantation); cumulative rates of severe chronic GVHD at 24 months were 11%, 12%, and 4%, respectively ($P < .05$ for those undergoing haploidentical donor *v* MUD and .062 for haploidentical donor *v* MRD transplantation).

NRM

Cumulative incidences of NRM are shown in Figure 2A. The respective rates of NRM for patients undergoing transplantation using MRDs, MUDs, and haploidentical donors were not significantly different at 12 (10%, 10%, and 4%, respectively) or 24 months (13%, 16%, and 7%, respectively).

Relapse of Malignancy

Cumulative incidences of relapse of malignancy were not significantly different among patients undergoing transplantation using the three donor groups (Fig 2B). For transplantation using MRDs, MUDs, and haploidentical donors, 24-month cumulative rates of relapse were 34%, 34%, and 33%, respectively.

Overall Survival and DFS

In the Cox analysis performed, transplantation groups were used as strata to allow for time-varying effects between any two types of transplantation. Age, diagnosis, Hematopoietic Cell Transplantation–Specific Comorbidity Index score, and CIBMTR disease-risk category were found to have a significant impact on survival (Table 2). For DFS, age, and CIBMTR disease-risk category were the only significant variables. Adjusted estimates of overall survival and DFS computed as average survival estimates of the pooled sample, weighted by the proportions of the significant variables in the Cox models, are shown in Figure 3. Survival was not significantly different for patients undergoing transplantation using the three types of donors. Adjusted 24-month estimated survival rates were 76%, 67%, and 64% for MRD, MUD, and haploidentical donor transplantation, respectively; adjusted rates of DFS were also similar between the three donor types (53%, 52%, and 60%, respectively, at 24 months). Similarly, global

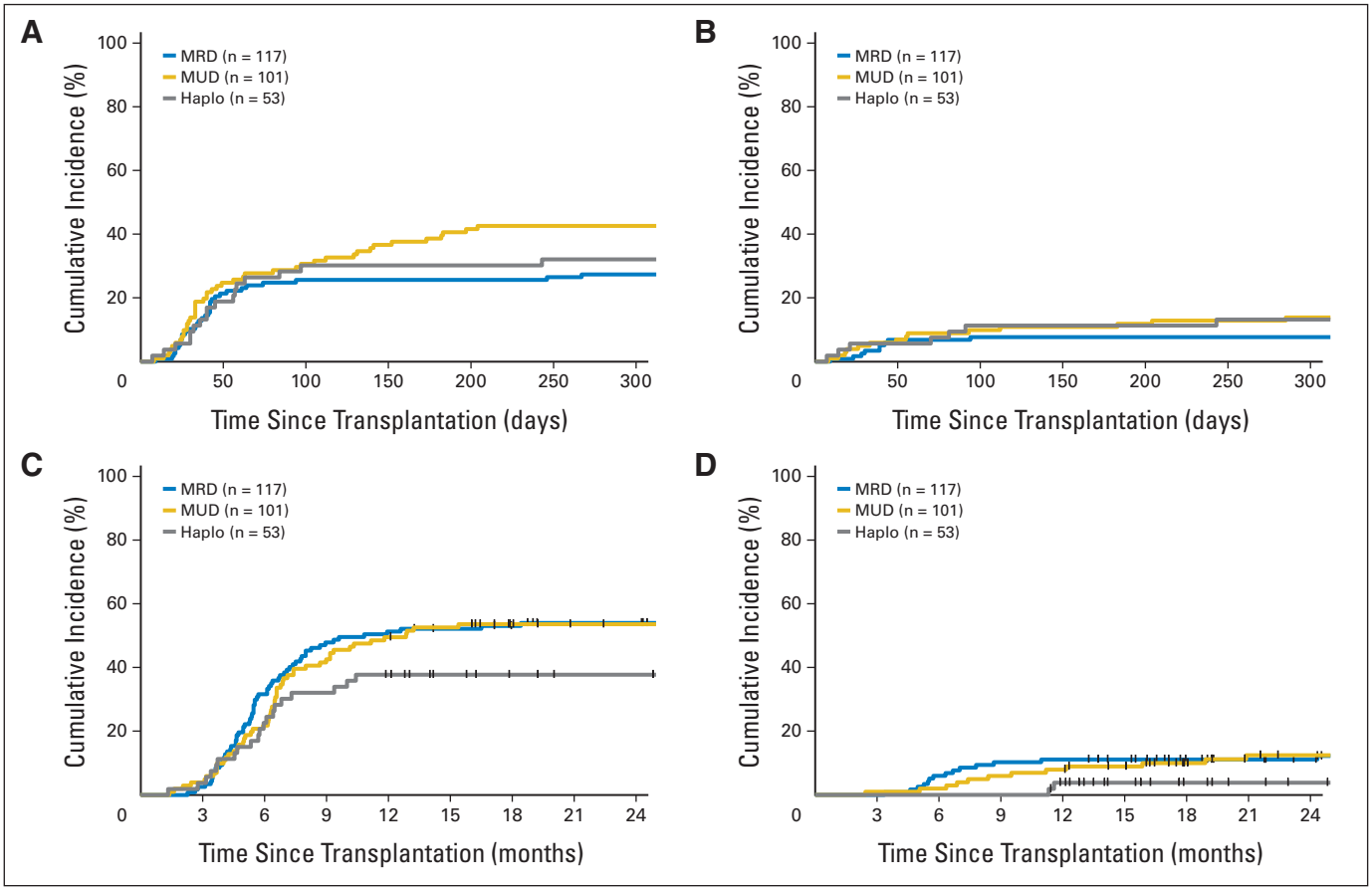

Fig 1. Cumulative incidence of graft-versus-host disease (GVHD) by donor type: (A) grades 2 to 4 acute GVHD, (B) grades 3 to 4 acute GVHD, (C) clinically extensive chronic GVHD, and (D) severe chronic GVHD by National Institutes of Health consensus criteria. Haplo, haploidentical donor; MRD, matched related donor; MUD, matched unrelated donor.

comparisons of overall survival and DFS also demonstrated no significant difference between the adjusted curves for transplantation performed using the different types of donors. Unadjusted curves for overall survival and DFS by donor group are provided in the Appendix for all patients (Appendix Fig A1, online only) and for specific diagnostic categories (Appendix Fig A2, online only).

PRS and Donor Lymphocyte Infusion

Ninety-four patients (35%) suffered relapse or progression of their malignancy at a median of 154 days after transplantation (range, 12 to 1,445 days; 40 patients undergoing MRD transplantation; 37, MUD; 17, haploidentical donor). Estimated PRS, assessed using the inverse probability of censoring weighted method, is shown in Figure

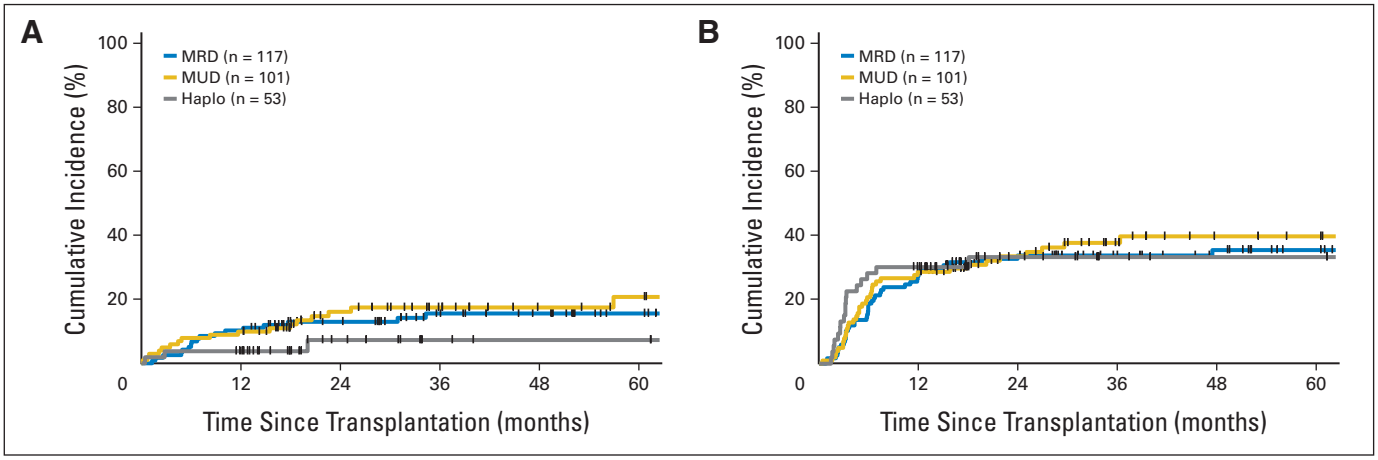

Fig 2. Cumulative incidence of nonrelapse mortality (NRM) and relapse of malignancy by donor type: (A) NRM and (B) relapse; both were analyzed as competing risks. Haplo, haploidentical donor; MRD, matched related donor; MUD, matched unrelated donor.

Table 2. Covariates With Significant Impact in Cox Analysis of OS and DFS

Covariate	HR	90% CI	*P*
OS			
HCTCI score (≥ 2 *v* 0 or 1)	1.74	1.18 to 2.54	.018
CIBMTR risk (high or intermediate *v* low)	1.84	1.17 to 2.88	.026
Diagnosis (ALL *v* other)	1.74	1.07 to 2.80	.059
Age	1.02	1.00 to 1.03	.087
DFS			
CIBMTR risk (intermediate or high *v* low)	1.50	1.07 to 2.11	.047
Diagnosis (ALL *v* other)	1.37	1.01 to 1.84	.086

NOTE. Significant impact defined as $P < .1$.
Abbreviations: ALL, acute lymphoblastic leukemia; CIBMTR, Center for International Blood and Marrow Transplant Research; DFS, disease-free survival; HCTCI, Hematopoietic Cell Transplantation–Specific Comorbidity Index; HR, hazard ratio; OS, overall survival.

4. PRS was significantly inferior for patients who experienced relapse after transplantation using a haploidentical donor than for those undergoing transplantation using other donor types. Estimated rates of PRS at 12 months were 67%, 63%, and 17% for MRD, MUD, and haploidentical donor transplantation ($P < .001$ for those undergoing haploidentical donor *v* MRD and MUD transplantation).

Six of 40 patients undergoing transplantation using MRDs, six of 37 patients undergoing transplantation using MUDs, and none of 17 patients undergoing transplantation using haploidentical donors who experienced relapse were treated with donor lymphocyte infusion (DLI; median initial CD3+ cell dose, 1×10^7/kg). PRS remained significantly different between the three donor groups, even if patients receiving DLI were excluded from analysis (2-month PRS: 64%, 76%, and 17% for MRD, MUD, and haploidentical donor transplantation, respectively; $P < .001$ for those undergoing haploidentical donor *v* MRD and MUD transplantation; Appendix Fig A3, online only).

DISCUSSION

To our knowledge, our study represents the first formal comparison of haploidentical donor transplantation with alloHCT using conventional MRDs and MUDs in an unselected population of patients undergoing first alloHCT for all hematologic malignancies. Although retrospective, strengths of this analysis include the contemporaneous population of patients studied, use of identical supportive care measures, and treatment within a single transplantation program. Furthermore, the primary outcome parameters—overall survival and DFS—were adjusted for potentially confounding patient-, disease-, and transplantation-related variables using a Cox proportional hazards analysis.

Our analysis suggests that incidence of NRM is not higher after haploidentical donor transplantation than after transplantation performed using conventional MRDs and MUDs. Indeed, a long-term NRM rate < 10% was achieved in the haploidentical donor patients (7% at 36 months). This finding is consistent with the low NRM seen in studies of nonmyeloablative T-cell–replete haploidentical donor transplantation performed using post-transplantation cyclophosphamide in multicenter settings.[5,7,18] Our analysis demonstrates that similar low rates of NRM can be achieved in an unselected population of patients undergoing both myeloablative and nonmyeloablative haploidentical donor transplantation performed using post-transplantation cyclophosphamide in a single institution.

The incidence and severity of clinical acute GVHD were not significantly different in patients undergoing transplantation using haploidentical donors when compared with patients undergoing transplantation using conventional donors. However, the incidence of extensive and severe chronic GVHD was significantly lower for haploidentical donor transplantation patients. The rates of acute and chronic GVHD observed after haploidentical donor transplantation in our unselected population were similar to those described in a series of 210 nonmyeloablative haploidentical donor transplantations reported by the Johns Hopkins group.[19] Bone marrow grafts have been demonstrated to cause less chronic GVHD than mobilized PBSC grafts in some randomized clinical trials[20,21] but not in others.[22,23] One meta-analysis in patients undergoing transplantation using MRDs showed a significantly higher incidence of both overall and extensive chronic GVHD in patients receiving PBSC grafts.[24] It is possible that the lower rate of chronic GVHD in the haploidentical donor transplantation patients may be explained by the greater use of bone marrow rather than PBSC grafts in this population. However, a direct relationship with use of T-cell–replete haploidentical donor grafts and post-transplantation cyclophosphamide cannot be excluded.

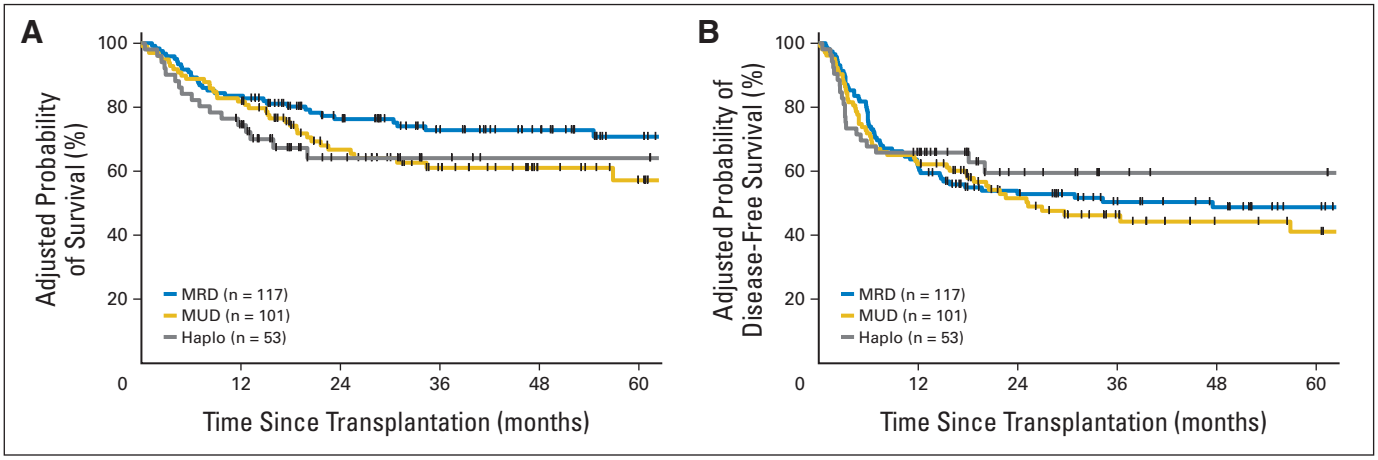

Fig 3. Adjusted estimated probabilities of (A) overall and (B) disease-free survival by donor type. Haplo, haploidentical donor; MRD, matched related donor; MUD, matched unrelated donor.

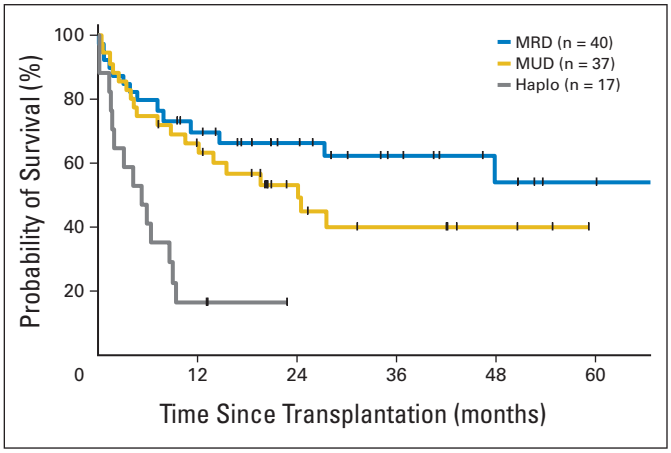

Fig 4. Estimated postrelapse survival assessed by the inverse probability of censoring weighted method. Haplo, haploidentical donor; MRD, matched related donor; MUD, matched unrelated donor.

Despite the less frequent use of myeloablative conditioning and PBSC grafts in the haploidentical donor transplantation patients, cumulative incidence of relapse of malignancy was not higher than cumulative incidence after conventional donor transplantation. Thus, adjusted DFS was not inferior in the haploidentical donor transplantation patients, with 60% of patients being alive and free of active malignancy at 2 years after haploidentical donor transplantation. Similarly, adjusted overall survival was not significantly different when haploidentical donor transplantation was compared with transplantation using conventional donors. T-cell–replete haploidentical donor transplantation has not previously been extensively compared with transplantation using conventional or alternative donor sources. In a comparison of nonmyeloablative transplantation performed for Hodgkin lymphoma in a multicenter setting, T-cell–replete haploidentical donor transplantation (n = 28) was found to have significantly lower NRM, equivalent overall survival, and improved PFS when compared with MRD (n = 38) and MUD (n = 24) transplantation.[18] Additionally, in two prospective parallel phase II trials conducted by the Blood and Marrow Transplant Clinical Trials Network, nonmyeloablative T-cell–replete haploidentical donor transplantation performed using post-transplantation cyclophosphamide was found to produce rates of overall and event-free survival similar to those achieved with nonmyeloablative double umbilical cord blood transplantation, with an NRM of 7% versus 24%, respectively.[5] Our study demonstrates that in an unselected population of patients undergoing transplantation contemporaneously for a variety of hematologic malignancies, including patients treated with myeloablative conditioning, T-cell–replete haploidentical donor transplantation with post-transplantation cyclophosphamide can produce long-term outcomes similar to those achieved with T-cell–replete transplantation using HLA-identical or well-matched MUD donors with conventional GVHD prophylaxis.

An unexpected finding from our study was that that survival after relapse of malignancy (ie, PRS) was inferior in patients undergoing transplantation using haploidentical donors compared with patients undergoing transplantation using MRDs or MUDs (12-month PRS, 17% *v* 67% and 63%, respectively). The factors underlying this finding are unclear. Because only 17 patients who underwent haploidentical donor transplantation experienced relapse, this finding should be approached with caution and needs to be confirmed in larger numbers of relapsing patients. This finding seems unrelated to the difficulty in administering DLI after relapse in patients who have undergone haploidentical donor transplantation. Administration of HLA-haploidentical DLI without post-transplantation cyclophosphamide may result in severe GVHD. Thus, no patient who relapsed after haploidentical donor transplantation received DLI, whereas DLI was administered in six patients who relapsed after MRD transplantation and six who relapsed after MUD transplantation. However, PRS remained inferior in the haploidentical donor transplantation patients, even when patients who received DLI were excluded from analysis (estimated 12-month survival, 64%, 76%, and 17% for MRD, MUD, and haploidentical donor transplantations, respectively; $P < .001$). It is also feasible that the inferior PRS observed in the haploidentical donor transplantation patients may be accounted for by a higher incidence of other risk features among these patients. However, the proportion of relapsing patients who underwent auto-transplantation before alloHCT was not significantly different among the three groups (seven [17.5%] of 40 patients undergoing MRD transplantation; eight [21.6%] of 37, MUD; three [17.5%] of 17, haploidentical donor).

In summary, this comparison suggests that outcomes after transplantation using haploidentical donors with post-transplantation cyclophosphamide are not inferior to those after conventional MRD and MUD transplantation. Transplantation using haploidentical donors with post-transplantation cyclophosphamide should be considered a valid alternative option for patients who need an alloHCT for whom no conventional donor is available.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Manuscript writing: All authors
Final approval of manuscript: All authors

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ORIGINAL REPORT

Two-Year Randomized Controlled Prospective Trial Converting Treatment of Stable Renal Transplant Recipients With Cutaneous Invasive Squamous Cell Carcinomas to Sirolimus

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ABSTRACT

Purpose
In light of the significant morbidity and mortality of cutaneous invasive squamous cell carcinomas (SCCs) in renal transplant recipients, we investigated whether conversion to sirolimus-based immunosuppression from standard immunosuppression could diminish the recurrence rate of these skin cancers.

Patients and Methods
In a 2-year randomized controlled trial, 155 renal transplant recipients with at least one biopsy-confirmed SCC were stratified according to age (< 55 *v* ≥ 55 years) and number of previous SCCs (one to nine *v* ≥ 10) and randomly assigned to conversion to sirolimus (n = 74) or continuation of their original immunosuppression (n = 81). Development of a new SCC within 2 years after random assignment was the primary end point.

Results
After 2 years of follow-up, the risk reduction of new SCCs in the multivariable analysis was not significant, with a hazard ratio (HR) of 0.76 (95% CI, 0.48 to 1.2; *P* = .255), compared with a non–sirolimus-based regimen. After the first year, there was a significant 50% risk reduction, with an HR of 0.50 (95% CI, 0.28 to 0.90; *P* = .021) for all patients together and an HR of 0.11 (95% CI, 0.01 to 0.94; *P* = .044) for patients with only one previous SCC. The tumor burden of SCC was reduced during the 2-year follow-up period in those receiving sirolimus (0.82 *v* 1.38 per year; HR, 0.51; 95% CI, 0.32 to 0.82; *P* = .006) if adjusted for the number of previous SCCs and age. Twenty-nine patients stopped taking sirolimus because of various adverse events.

Conclusion
Conversion to sirolimus-based immunosuppression failed to show a benefit in terms of SCC-free survival at 2 years.

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INTRODUCTION

The reported cancer risk in renal transplant recipients (RTRs) is two- to six-fold greater than in the general population.[1-3] Cutaneous squamous cell carcinomas (SCCs) are the most common post-transplantation cancers, occurring 65 to 250 times more often than in the general population.[4-6] Invasive SCC may derive from SCC in situ (Bowen's disease) or other intraepidermal precursor lesions (actinic keratoses) and may metastasize.[4] The cumulative incidence of cutaneous SCC ranges from 2% to 24% after 5 years post-transplantation.[5,7] Once an individual develops a first SCC, the risk of developing subsequent independent SCCs is high.[8,9] In addition to the clinical and economic burdens of multiple SCCs, transplantation skin cancers carry a worse prognosis than those from immunocompetent persons, with more aggressive behavior and increased mortality resulting from metastatic disease.[10]

Etiologic causes of cutaneous SCCs in RTRs include: exposure to ultraviolet radiation, reduced immunosurveillance, skin type, age at transplantation, and human papillomavirus infection.[4,11-13] The intensity and duration of immunosuppressive therapy influence SCC risk, resulting in increased incidence in cardiac compared with renal or liver transplant recipients.[14,15] There is also compelling evidence for carcinogenic mechanisms associated with cyclosporine[16-18] and azathioprine.[19]

The antiproliferative response of mammalian target of rapamycin (mTOR) inhibitors may confer a lower risk of the development of malignancy, as shown in small pilot studies and short-term registry analyses.[20-22] Sirolimus interferes with intracellular proteins, with influences on angiogenesis, cell growth, division, and survival.[23] In addition, sirolimus has been shown to inhibit the ultraviolet B activation of metalloproteinases that may promote cancer formation and premature skin aging.[24] Prospective randomized studies comparing efficacy of sirolimus with that of other immunosuppressive regimens have indicated a tendency for fewer skin tumors developed in the sirolimus group as a secondary outcome measure.[20,22] Until recently, there has been a lack of prospective randomized studies of mTOR inhibitors evaluating the recurrence rate of cutaneous SCC as the primary outcome measure. A study in Australia included 86 patients with either SCC or basal cell carcinoma (BCC).[25] At 1 year, there was a reduction in formation of new SCCs, of which most were SCC in situ. The incidence and pattern of skin tumors in Australia, however, is different from those in Western Europe because of differences in ultraviolet light exposure, which may affect the influence of sirolimus conversion.[12] In the RESCUE (Recurrent Cutaneous Squamous Cell Carcinoma Under Rapamune) study, a 2-year randomized, prospective, open-label, multicenter trial, we investigated whether conversion to sirolimus-based immunosuppression in long-term RTRs would diminish the rate of new cutaneous invasive SCCs.

PATIENTS AND METHODS

Patients Studied

RTRs were recruited from five transplantation centers in the Netherlands and 16 in the United Kingdom. Inclusion criteria included: first or second kidney transplantation with ≥ one biopsy-confirmed cutaneous invasive SCC, age ≥ 18 years, > 12 months post-transplantation, stable graft function (estimated glomerular filtration rate ≥ 20 mL/min), receiving maintenance calcineurin inhibitor, azathioprine, mycophenolate, and/or steroids for at least 12 weeks before random assignment, and no acute rejection episode within 12 weeks before random assignment.

Exclusion criteria included: metastatic cutaneous SCC, internal malignancies (documented after transplantation), serum creatinine at screening increased > 30% above baseline, total WBC count < 3,000/μL, platelet count < 75,000/μL, fasting-triglycerides > 3.95 mmol/L, cholesterol > 7.8 mmol/L (± statins), transaminases > 2× above normal, planned/present pregnancy, evidence of systemic infection or HIV infection at random assignment, or Fitzpatrick skin type V to VI.

The independent ethics committee or institutional review board of each site approved the protocol. Participants provided written informed consent in accordance with the Declaration of Helsinki.

Random Assignment

After patient consent, random assignment took place using blinded envelopes containing treatment codes for either continuation of maintenance therapy or conversion to sirolimus. Random assignment (1:1) was stratified by transplantation center, number of biopsy-confirmed SCCs (<10 v ≥ 10) before random assignment, and recipient age (< 55 v ≥ 55 years). For each of the defined stratification groups, random assignment envelopes with a fixed random assignment order per stratum were available with a number of four per random assignment block.

Procedures

The target blood level of sirolimus was 5 to 10 ng/mL; sirolimus was started the day the purine antagonist (azathioprine or mycophenolate mofetil) and/or calcineurin inhibitor (cyclosporine or tacrolimus) was withdrawn (loading dose, 8 mg; maintenance dose, 4 mg). Between days 5 to 7, a sirolimus trough level was measured and the dose adjusted to the defined range. All patients were also treated with at least 5 mg of prednisone daily. The immunosuppressive regimen was not changed in the control patients. At regular three monthly intervals, a complete skin inspection was undertaken by the dermatologist, and renal function and adverse events were monitored by the nephrologist. The dermatologists were blinded for the treatment arm, but patients and their nephrologists were unblinded.

Skin lesions clinically suspected to be invasive SCCs or BCCs were biopsied for histologic interpretation by the local dermatopathologists. In RTRs, actinic keratose and SCC in situ are clinically difficult to discern, and these lesions were not routinely biopsied. Only biopsy-confirmed invasive SCCs, SCCs in situ, and BCCs were included in the study.

Laboratory data were recorded every 3 months. Adverse events were evaluated during the study period, and the reasons for dropout were documented.

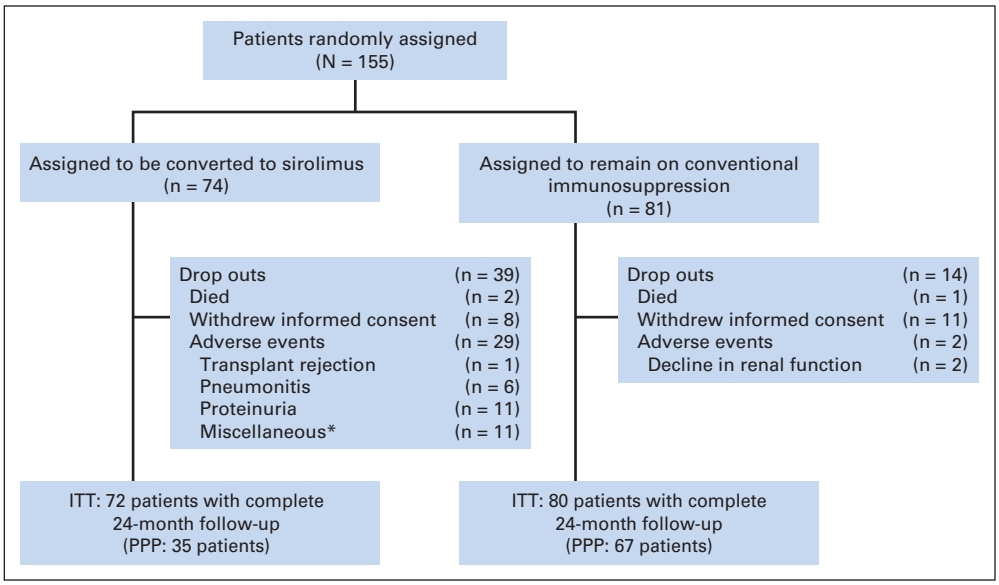

Fig 1. Patient disposition. ITT, intention to treat; PPP, per-protocol population. (*) Slow wound healing (n = 1), pulmonary embolus (n = 1), pneumonia (n = 1), edema (n = 2), diarrhea (n = 2), fatigue (n = 1), skin rash (n = 1), dyslipidemia (n = 1), and diabetes mellitus (n = 1).

The development of cutaneous invasive SCC within 2 years after conversion was the primary end point of this study. Secondary end points included: incidence, severity, and reversibility of biopsy-confirmed acute rejection episodes; patient and graft survival; and renal function 2 years after random assignment.

Statistical Analyses

Sample size calculation was based on a 50% risk to develop a subsequent cutaneous invasive SCC in a 2-year period, which has been reported earlier.[8,9] In addition, a relative risk reduction of 50% was expected in the patients assigned to be converted to sirolimus compared with patients who would continue their original immunosuppressive regimen, based on results obtained on new skin lesions in de novo patients.[20] To detect a difference in recurrence probability at 2 years of 50% versus 25% at a two-sided alpha level of 5% and a power of 0.9, assuming 25% loss to follow-up, 154 patients would be needed. Hence, we aimed at 80 patients per arm (NCSS Statistical Software; NCSS, Kaysville, UT).

The occurrence of SCC was assessed with Kaplan-Meier curves and Cox regression to calculate the hazard ratio (HR). The annualized per-patient SCC recurrence rate was modeled using a negative binomial regression model. All RTRs were included in the intention-to-treat (ITT) analyses and observed during the 2-year follow-up period or until death. The same analyses were performed for the first year and stratified for one previous SCC or > one SCC. We also performed per-protocol population (PPP) analyses including the RTRs until they dropped out because of adverse events or withdrew informed consent (Fig 1).

First analyses (Table 1) showed that sex was imbalanced despite random assignment ($P = .003$), but this did not affect the other analyses. The unexpected low recruitment rate in two thirds of centers in the United Kingdom, in combination with the fixed order per stratum, resulted in the imbalance of the stratification factors. To analyze the impact of this imbalance on treatment outcome, we performed multivariable analyses and analyses stratified for sex, age at random assignment, immunosuppressive drugs, and country. Finally, adjustments were only made for age and number of invasive SCCs before inclusion, the predefined characteristics for which we had stratified. For the analyses, we used the PASW Statistics software package (release 17.02; SPSS, Chicago, IL).

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	Patients Converting to Sirolimus (n = 74)		Patients Continuing Original Immunosuppression (n = 81)	
	No.	%	No.	%
Sex*				
Female	32	43	17	21
Male	42	57	64	79
Age at random assignment, years				
< 55	31	42	23	28
≥ 55	43	58	58	72
Functioning transplant at random assignment, years				
Mean	19		18	
SD	8		7	
Serum creatinine, μmol/L				
Mean	121		137	
SD	44		48	
Immunosuppressive regimen at random assignment				
One immunosuppressive drug ± prednisone	63	85	64	79
Aza	42		33	
MMF	10		3	
Cyclosporine	7		21	
Tacrolimus	4		7	
Two immunosuppressive drugs ± prednisone	11	15	17	21
Calcineurin inhibitor with Aza	9		13	
Calcineurin inhibitor with MMF	2		4	
Skin type (Fitzpatrick I to IV)				
I (very fair skin; Celtic)	9	12	9	11
II	39	53	44	54
III	26	35	25	31
IV (darker skin; Mediterranean)	0	0	3	4
No. of invasive SCCs before random assignment				
1	30	40	23	29
2 to 9	33	45	52	64
≥ 10	11	15	6	7

Abbreviation: Aza, azathioprine; MMF, mycophenolate mofetil; SCC, squamous cell carcinoma; SD, standard deviation.
*Sex was imbalanced despite random assignment ($P = .003$), but this did not affect additional analyses.

RESULTS

We included 103 RTRs in the Netherlands and 52 in the United Kingdom between January 2004 and September 2009. The pathway of patients recruited and outcomes are shown in Figure 1. Demographic and baseline characteristics are presented in Table 1.

The Kaplan-Meier analysis of all 155 randomly assigned patients showed separation between the curves, but after 2 years, there was no significant difference for invasive SCC-free survival ($P = .155$; Figs 2A to 2C). In exploratory analyses at 1 year, statistical significance was still present ($P = .006$; Fig 2D). Sirolimus was especially effective during the first year after conversion in RTRs with only one previous SCC. In this subgroup, only one of 30 patients developed a new SCC 9 months after conversion compared with six of 23 patients in the control group ($P = .015$; Fig 2E). Conversion to sirolimus was much less effective in patients with multiple SCCs before inclusion (Figs 2C, 2F).

In multivariable analyses, the HR for SCC recurrence with sirolimus was 0.76 (95% CI, 0.48 to 1.2; $P = .255$) after the 2-year follow-up period, representing a statistically nonsignificant 24% reduction in the estimated risk of developing at least one subsequent invasive SCC. In exploratory analyses at 1 year, the HR was 0.50 (95% CI, 0.28 to 0.90; $P = .007$), a significant 50% reduction after the first year of follow-up (Table 2). The ITT and PPP crude and adjusted analyses for invasive and/or in situ SCCs are summarized in Appendix Table A1 (online only). The analyses of in situ SCCs resembled those of invasive SCCs, and the PPP analyses showed a slightly stronger risk reduction than the ITT analyses (Appendix Table A1, online only). A total of 15 patients (20.3%) converted to sirolimus, and 27 (33.3%) of those continuing their original immunosuppression developed ≥ one BCC, which resulted in an HR for BCC recurrence with sirolimus of 0.56 (95% CI, 0.30 to 1.1; $P = .076$) and an adjusted HR of 0.67 (95% CI, 0.34 to 1.3; $P = .233$).

The annualized per-patient invasive SCC recurrence rate is shown in Appendix Table A2 (online only); it was 0.82 in the sirolimus arm compared with 1.38 in controls. The relative risk for developing an invasive SCC was 0.60 (95% CI, 0.35 to 1.0; $P = .057$) and was 0.51 (95% CI, 0.32 to 0.82) when adjusting for

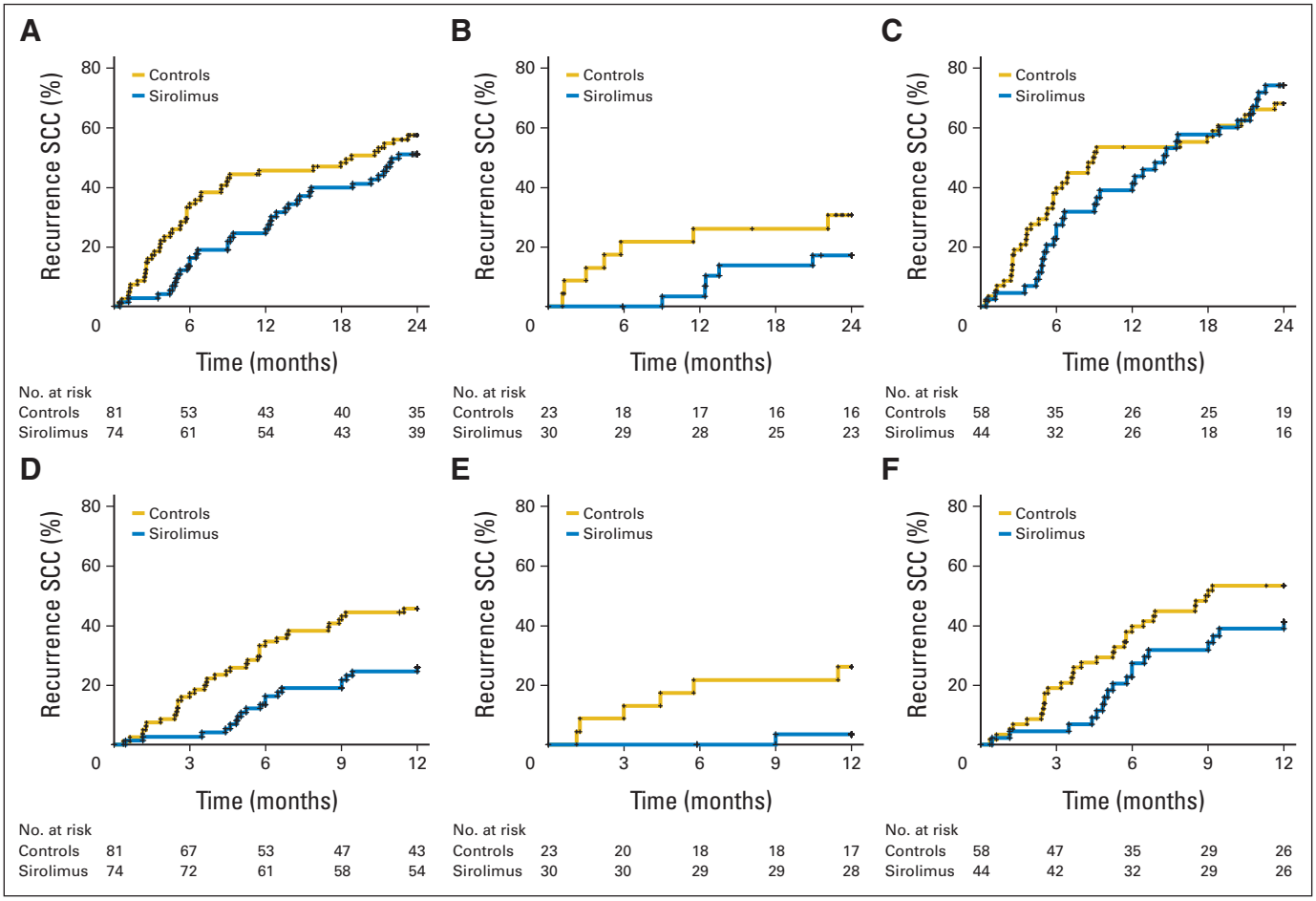

Fig 2. Recurrence of squamous cell carcinoma (SCC) in patients converting to sirolimus and control patients who continued their original immunosuppressive regimen according to the intention to treat analysis. (A) Follow-up until 2 years (primary end point for all patients together; $P = .155$) and (B) stratified for one SCC at inclusion ($P = .193$) or (C) ≥ one SCC at inclusion ($P = .854$). (D) Follow-up until 1 year for all patients together ($P = .006$) and (E) in patients with one SCC ($P = .015$) and (F) > one SCC ($P = .139$).

number of SSCs at inclusion and age, a 49% reduction in the risk of developing an SCC compared with a non–sirolimus-based regimen. The adjusted and PPP analyses showed stronger risk reductions (Table A2, online only).

The first sirolimus trough level (± standard deviation [SD]) was 12.0 ± 6.4 ng/mL, measured after a mean (± SD) of 10.6 ± 6.4 days, and higher in patients who discontinued sirolimus (13.1 ± 6.8 *v* 10.9 ± 5.6; $P = .149$). Mean trough levels (± SD) were 9.4 ± 4.5, 7.8 ± 2.4, and 7.1 ± 1.9 ng/mL at 3, 12, and 24 months, respectively. Within these ranges, sirolimus trough levels did not significantly predict the risk for recurrent SCCs and were also not significantly associated with adverse effects or treatment discontinuation (data not shown).

In the sirolimus arm, eigth RTRs (10.8%) withdrew consent after a median time of 3.5 months (range, 0.99 to 11.8 months), compared with 11 (13.6%) after 8.4 months (range, 0.03 to 21.2 months) in controls (Fig 1). As expected in stable RTRs receiving immunosuppression for a mean of 18 years, there were fewer treatment-related adverse events in the patients who continued their original immunosuppression. Two RTRs in this group had a decline in renal function, which was not treatment related, after 10.6 and 12.8 months, respectively; one died after 16.1 months (cause unknown; Fig 1). In contrast, a total of 29 converted patients (39.1%) had to discontinue sirolimus because of adverse effects after a median time of 5.6 months (range, 0.69 to 18.0 months) or because of death resulting from a cerebrovascular accident after 5.9 months or from metastatic SCC after 6.6 months. One patient developed a borderline rejection with additional signs of chronic allograft nephropathy on a renal biopsy 6 months after conversion. After treatment, serum creatinine stabilized at 300 μmol/L (175 μmol/L at conversion). Other adverse effects are summarized in Table 3.

Among the patients who finished the protocol on therapy in both treatment arms, serum creatinine did not change during the study period (control arm: start, 133 ± 49 μmol/L; end, 135 ± 51 μmol/L; sirolimus arm: start, 115 ± 38 μmol/L; end, 111 ± 37 μmol/L [± SD]). In addition, proteinuria did not change during the study period (control arm: start, 0.3 ± 0.2 g/d; end, 0.4 ± 0.6 g/d; sirolimus arm: start, 0.5 ± 1.4 g/d; end, 0.4 ± 0.4 g/d [± SD]), although 11 of the included patients stopped using sirolimus mainly because of proteinuria. Other laboratory investigations (cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, hemoglobin A1c, albumen, hemoglobin, leukocytes, and platelets) remained stable between start and end of the study.

Table 2. Risk for Developing ≥ One Subsequent SCC

Factor	Recurrence at 2-Year Follow-Up*					
	Univariate			Multivariable†		
	HR	95% CI	*P*	HR	95% CI	*P*
Sirolimus conversion	0.73	0.47 to 1.1	.157	0.76	0.48 to 1.2	.255
Age (per 10 years)	0.90	0.73 to 1.1	.304	0.95	0.77 to 1.2	.610
Male *v* female	0.94	0.60 to 1.5	.781	0.97	0.59 to 1.6	.886
No. of previous SCCs						
1	1			1		
2 to 9	4.2	2.2 to 7.8	.000	3.9	2.1 to 7.4	.000
≥ 10	7.2	3.3 to 15.7	.000	7.3	3.3 to 16.1	.000
	Recurrence at 1-Year Follow-Up‡					
	Univariate			Multivariable†		
	HR	95% CI	*P*	HR	95% CI	*P*
Sirolimus conversion	0.47	0.27 to 0.81	.007	0.50	0.28 to 0.90	.021
Age (per 10 years)	0.88	0.69 to 1.1	.333	0.89	0.69 to 1.1	.339
Male *v* female	1.5	0.79 to 2.7	.229	1.4	0.73 to 2.6	.321
No. of previous SCCs						
1	1			1		
2 to 9	4.1	1.8 to 9.2	.001	3.6	1.6 to 8.2	.002
≥ 10	7.3	2.8 to 18.9	.000	7.9	3.0 to 20.6	.000
	Stratified for Patients With One and > One SCC‡§					
	Recurrence at 1-Year Follow-Up			Recurrence at 2-Year Follow-Up		
	HR	95% CI	*P*	HR	95% CI	*P*
One SCC	0.11	0.01 to 0.94	.044	0.48	0.15 to 1.5	.203
> One SCC	0.65	0.36 to 1.2	.144	0.96	0.60 to 1.5	.854

Abbreviations: HR, hazard ratio; SCC, squamous cell carcinoma.
*Primary end point.
†Multivariable analyses included sirolimus conversion, age, sex and 3 categories of numbers of squamous cell carcinomas at inclusion of the study.
‡Exploratory analyses.
§Univariate analysis.

DISCUSSION

Cutaneous invasive SCC is a serious complication of long-term organ transplantation, with significant morbidity, along with mortality rates similar to those seen with post-transplantation lymphoproliferative disease.[4] The primary analysis in this study showed that conversion to sirolimus-based immunosuppression resulted in a nonsignificant 24% reduced risk of a new cutaneous invasive SCC developing within 2 years after conversion. The exploratory analysis at 1 year resulted in a significant 50% risk reduction. There was a 49% reduction in risk of developing multiple invasive SCCs. Comparable risk reductions were observed for SCC in situ and BCC. The effect of conversion to sirolimus was especially eminent in patients with only one previous SCC at the time of conversion.

These results are similar to the preliminary findings of a small pilot study from Germany, in which only one of 16 RTRs in the sirolimus conversion group compared with eight of 17 in the control group developed a skin cancer within 12 months of conversion.[26] This study included all forms of nonmelanoma skin cancer and did not require the participant to have had previous skin cancer. A study from Australia included 86 patients with either SCC or BCC.[25] There was a reduction in formation of new SCCs (most of which were SCC in situ) per year from 1.71 in the control group to 0.88 in the sirolimus group in the first year after conversion. The time since transplantation was much shorter (mean, 9.1 years), and skin cancers were mostly SCC in situ, not invasive SCC.[25] A recent study from France included 120 patients with SCC and found a 44% risk reduction of new SCCs at 2 years.[27] Efficacy was restricted to RTRs with only one previous SCC, and the difference remained significant at 2 years. The French study included more patients with only one SCC (55% *v* our 34%), and analysis occurred earlier after transplantation (12 *v* 18 years). In the first year after conversion, we observed a comparable benefit for the risk of recurrent SCC.

The patient population included in our trial comprised a high-risk group for recurrent SCCs. In contrast to previous studies,[25,27] our 2-year results indicated that conversion to sirolimus did not prevent the occurrence of new SCCs. This conclusion is in line with observations that with time, new SCCs occur earlier and are more often multiple.[8-10] Duration of immunosuppressive therapy influences SCC risk, with compelling evidence for the carcinogenic mechanisms associated with cyclosporine[16-18] and azathioprine.[19] In addition, the impact of withdrawal of the calcineurin inhibitor and/or azathioprine may be more beneficial in patients earlier in their post-transplantation course (ie, those with only one SCC).

The impact on skin cancer risk reduction observed in our study was attenuated by the 42% discontinuation rate of sirolimus because of adverse effects. This is similar to the discontinuation rates of 35% in

Table 3. Adverse Events Not Leading to Discontinuation of Treatment

Adverse Event	Patients Converting to Sirolimus (No.)	Patients Continuing Original Immunosuppression (No.)
Infection		
Respiratory	17	6
Urinary	3	4
Abdominal	2	1
Septicemia	1	1
Skin	14	9
Other	6	0
Other		
Pneumonitis	1	0
Proteinuria	5	0
Skin		
Rash	5	1
Acne	3	0
Diarrhea	7	0
Aphthous stomatitis	4	0
Flu-like symptoms	2	0
Fatigue	1	1
Edema	7	2
Deep venous thrombosis	1	1
New onset diabetes mellitus	0	1
Dyslipidemia (total cholesterol > 7.8 mmol/L)	13	3
Thrombocytopenia (< 100,000/μL)	2	3
Leukopenia (< 4000/μL)	11	5

the Australian study[25] and 25% in the French study[27] and to rates observed in trials designed to investigate the nephron-sparing potential of mTOR inhibitors.[28,29] Several factors contributed to this high discontinuation rate. First, the protocol was designed in 2004 and included a loading dose (8 mg) and initial maintenance dose (4 mg), resulting in high levels in certain individuals with an increased risk of early toxicity. Subsequent studies, along with clinical practice, abandoned the loading dose and used lower maintenance doses and target levels. In addition, investigators in the early phase of this trial were cautious about the risk of secondary proteinuria and pneumonitis. The combination of high initial sirolimus levels and investigator caution led to early discontinuation of sirolimus in several participants with mild to moderate proteinuria and other adverse effects who may have responded to dose adjustment and/or the addition of an angiotensin-converting enzyme inhibitor.[30] To prevent high initial sirolimus levels, we now recommend discontinuing the purine antagonist and/or calcineurin inhibitor and commencing sirolimus 2 to 3 mg once daily the next day. Alternatively, gradual conversion over weeks or months with lower initial dosing could result in a more tolerable regimen, but this carries the risk of drug-drug interactions, especially with cyclosporine.

There was no significant change in renal function or increase in proteinuria in the patients who continued sirolimus treatment, suggesting the safety of sirolimus conversion in RTRs many years post-transplantation. There were no deaths related to conversion, but six patients (8%) developed pneumonitis, which resolved with drug cessation (Fig 1); one patient with pneumonitis recovered despite continued treatment with sirolimus (Table 3). This serious complication is rare, but frequency may have been increased in this study as a result of of initial higher sirolimus doses, because most cases occurred within a few weeks of sirolimus initiation.[28]

The incidence of skin malignancies in RTRs increases progressively with intensity and duration of immunosuppression and therefore with overall time since transplantation. Prospective cohort studies in transplant recipients have defined risk factors for skin cancer development that are clinically robust, allowing reliable identification of patients at highest risk of future skin malignancies who may benefit from early conversion to sirolimus.[8,9] The results of our and other studies examining reduction of skin and nonskin malignancies suggest a benefit in early conversion to sirolimus-based maintenance regimens. Such a proactive rather than reactive policy carries the additional benefit of reducing calcineurin inhibitor–induced progressive loss of renal function, both in RTRs and non–renal organ transplant recipients.[31] In patients with proteinuria and/or already compromised renal allograft function, conversion to an mTOR inhibitor is no longer a valid option.[22]

There are limitations to our study. As experienced by others, recruitment of the patients was unexpectedly difficult. The randomization procedure was implemented correctly, but recruitment of only one or two patients in several centers, in combination with the fixed order per stratum, jeopardized balanced random assignment. In addition, there were differences between the groups regarding the use of azathioprine and/or cyclosporine. Azathioprine in particular has been associated with the more frequent occurrence of SCC and/or may indicate a longer time after transplantation. However, the differences between the groups in the current cohort were not statistically significant, and adjustment had no impact on the results of the analyses.

In conclusion, conversion to low-dose mTOR inhibition with careful monitoring was not associated with increased risk of transplant dysfunction. However, in our study population, comprising patients with one or more previous SCCs, there was no benefit at 2 years in converting RTRs in terms of SCC-free survival. Conversion in those with only one previous SCC should be carefully balanced against toxicities that can lead to relatively high dropout rates. The benefit afforded by the mTOR-based regimen after conversion in the subgroup of patients with only one previous invasive SCC[27] may suggest that an mTOR inhibitor has the potential to become an effective early immunosuppressive strategy to reduce the risk of cutaneous SCC in RTRs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ORIGINAL REPORT

Lack of Specificity of Plasma Concentrations of Inhibin B and Follicle-Stimulating Hormone for Identification of Azoospermic Survivors of Childhood Cancer: A Report From the St Jude Lifetime Cohort Study

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ABSTRACT

Purpose
Many male survivors of childhood cancer are at risk for azoospermia. Although both the levels of follicle-stimulating hormone (FSH) and inhibin B are correlated with sperm concentration, their ability to predict azoospermia in survivors of childhood cancer remains uncertain.

Patients and Methods
Semen analysis was performed and serum levels of FSH and inhibin B were measured in 275 adult male survivors of childhood cancer who had received gonadotoxic therapy. Receiver operating characteristic (ROC) analysis was performed to determine the optimal inhibin B and FSH values for identifying patients with azoospermia. The patient sample was divided into a learning set and a validation set. Sensitivity, specificity, and positive and negative predictive value were calculated.

Results
Inhibin B was dichotomized as ≤ 31 ng/L or more than 31 ng/L and FSH was dichotomized as ≤ 11.5 mIU/mL or more than 11.5 mIU/mL based on results of the ROC analysis. Using these values, the specificity of the serum level of inhibin B for identifying azoospermic survivors was 45.0%, and the positive predictive value was 52.1%. The specificity for FSH was 74.1%, and the positive predictive value was 65.1%.

Conclusion
Neither serum inhibin B nor FSH is a suitable surrogate for determination of sperm concentration in a semen sample. Young men and their physicians should be aware of the limitations of these measures for assessment of fertility potential.

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INTRODUCTION

The treatment of children and adolescents with cancer has become increasingly successful. Approximately 80% of all patients diagnosed before 15 years of age will survive for five years. The majority are expected to survive for many years after diagnosis.[1] In boys and young men, irradiation of the gonads and/or the use of certain classes of chemotherapeutic agents (eg, alkylating agents) may damage spermatogenesis leading to impaired fertility.[2]

Adult survivors of childhood cancer place high value on fertility and desire information regarding their potential to sire/conceive a pregnancy.[3,4] Semen analysis is a noninvasive method for estimation of male fertility potential, but religious, cultural, and personal barriers may deter individuals from completing the procedure.[5]

Inhibin B is a dimeric protein that consists of alpha and beta subunits that are synthesized in the Sertoli cells of the testis.[6] The level of inhibin B is inversely related to the level of follicle-stimulating hormone (FSH) in normal males and those with a variety of reproductive abnormalities.[7] Jensen et al[8] reported that the serum level of inhibin B was directly related, whereas the serum level of FSH was inversely related, to sperm concentration in healthy Danish males. Others have reported that the serum inhibin B level is highly correlated with sperm concentration among men undergoing evaluation for male factor infertility.[9-11] Studies of the relationship between serum levels of inhibin B and FSH and

sperm concentration in adult survivors of childhood cancer have been limited in the number of evaluated patients who received gonadotoxic treatment and/or the number of patients from whom semen samples were obtained.[12-14]

We undertook these analyses to determine the sensitivity, specificity, and positive and negative predictive value of the serum levels of inhibin B and FSH for the identification of azoospermia. This assessment is possible because of the availability of a large population of long-term survivors of childhood cancer who had been treated with alkylating agents, direct gonadal irradiation (any dose), and/or hypothalamic/pituitary irradiation (≥ 40 Gy), all of which are associated with a significant risk of azoospermia.[15]

PATIENTS AND METHODS

A cohort of patients (St. Jude Lifetime Cohort Study [SJLIFE]) was identified that fulfilled the following criteria: diagnosis of childhood malignancy treated at St. Jude Children's Research Hospital (SJCRH), survival ≥ 10 years from diagnosis, and current age ≥ 18 years. The detailed methods used for ascertainment, recruitment, and evaluation of the members of this cohort have been reported previously.[16] This investigation was approved by the institutional review board at SJCRH, and all participants and/or their legal guardians provided informed consent.

The cumulative doses for 32 specific chemotherapeutic agents (5-azacytidine, bleomycin, busulfan, carboplatin, carmustine, cisplatinum, cyclophosphamide [intravenously [IV] or orally], cytarabine [IV, intramuscularly, intrathecally, subcutaneously], dacarbazine, dactinomycin, daunorubicin, dexamethasone, doxorubicin, etoposide [IV, orally], fludarabine, fluorouracil, hydroxyurea, idarubicin, ifosfamide, L-asparaginase, lomustine, melphalan, methotrexate [IV, intramuscularly, intrathecally], nitrogen mustard, prednisone, procarbazine, teniposide, thioguanine, thiotepa, tretinoin, vinblastine, vincristine), surgical procedures, and radiation treatment fields, dose, and energy source were abstracted from the medical records according to a protocol similar to that used in the Childhood Cancer Survivor Study (CCSS).[17]

Participants underwent a risk-based assessment as suggested by the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer (COG Guidelines).[18] Semen analysis was offered to men who had received potentially gonadotoxic treatment, including exposure to an alkylating agent, direct testicular irradiation (any dose), or hypothalamic/pituitary irradiation (≥ 40 Gy). FSH was to be measured in all men who received gonadotoxic therapy, and inhibin B was to be determined in all men who underwent semen analysis. Those who had received hypothalamic/pituitary irradiation ≥ 40 Gy or had a tumor in the hypothalamic/pituitary region (eg, craniopharyngioma) and those who were receiving exogenous androgen treatment were excluded from these analyses. Eleven participants had undergone unilateral orchiectomy. No participant underwent bilateral orchiectomy.

Inhibin B and FSH Analyses

To analyze the serum hormone levels, we obtained morning peripheral blood samples and separated the serum. The serum samples were stored in liquid nitrogen at −180° Celsius until they were shipped on dry ice to Quest Diagnostics (Valencia, CA) for inhibin B analysis by immunoassay. The lower limit of the assay is 30 ng/L.

Serum FSH was assayed by using a two-step sandwich-type electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN) in the SJCRH clinical laboratory. Within-assay coefficient of variation (CV) was 1.2% (n = 20; mean, 4.72 mIU/mL). Day-to-day imprecision for three control materials (Liquichek Immunoassay Plus Control, Trilevel; Bio-Rad Laboratories, Hercules, CA) was as follows: Level 1, n = 155; mean, 7.33 mIU/mL; CV, 3.9%; Level 2, n = 155; mean, 19.72 mIU/mL; CV, 3.7%; Level 3, n = 150; mean, 46.65 mIU/mL; CV, 3.7%. The normal range for males age 20 to 50 years in the SJCRH laboratory is 2.0 to 9.2 mIU/mL.

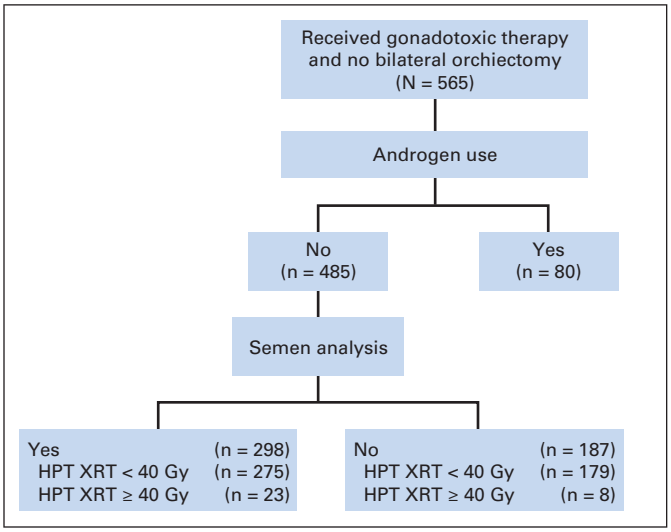

Fig 1. CONSORT diagram showing patient population from which semen analysis data were derived. HPT XRT, hypothalamic-pituitary irradiation.

Semen Analysis

The semen samples were collected after a minimum of 2 days and a maximum of 7 days of sexual abstinence and were processed within 30 minutes of collection following the WHO Guidelines, 5th Edition.[19] Every semen sample was allowed to liquefy, and the time to liquefaction was recorded. The raw sample was microscopically evaluated. If no sperm were detected, the sample was centrifuged and concentrated. The concentrated sample was again evaluated before it was considered azoospermic. A recent medical history was taken at the time of collection and, if any historical issues were revealed (recent fever above 102°F, certain medication use, recent genitourinary tract infection, or injury), a request for a repeat specimen in 1 month to confirm azoospermia was made.

Statistical Analysis

Receiver operating characteristic (ROC) analysis was undertaken to identify the optimal dichotomization values for FSH, inhibin B, and the inhibin B:FSH ratio for identifying patients with azoospermia. Specifically, the patient sample was divided into a learning set (n = 140) and a validation set (n = 135) by random assignment. The ROC analysis was performed by using PROC LOGISTIC in SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Study Population

Two hundred ninety-eight (53%) of 565 SJLIFE males who received gonadotoxic treatment, were not receiving exogenous androgens, and participated in SJLIFE before February 23, 2011, submitted a semen specimen for evaluation (Fig 1). Of these 298, we excluded those who had received ≥ 40 Gy hypothalamic/pituitary irradiation and/or had a tumor in the hypothalamic/pituitary region (n = 23), for a total of 275 eligible cases. The majority were non-Hispanic white and had at least a high school education. The most frequent diagnosis was acute lymphoblastic leukemia (Table 1). The median age at semen analysis was 30.5 years (range, 19.7 to 59.1 years). Inhibin B was measured in 238 and FSH in 275 participants. One hundred five (38.2%) of 275 were found to be azoospermic. Most of those who submitted semen specimens reported that they had no children (Appendix Table A1, online only). Among those who did not submit semen specimens, live births were reported by one participant who did

Table 1. Demographic Characteristics for Study Patients

Characteristic	No. of Patients	%
Race/ethnicity		
Non-Hispanic white	242	88.0
Non-Hispanic black	28	10.2
Other	5	1.8
Education		
No high school or GED	17	6.2
High school or GED	67	24.4
Some college; no bachelor's degree	96	34.9
Bachelor's degree or higher	89	32.4
Missing	6	2.1
Age at diagnosis, years		
> 0- < 5	109	39.6
≥ 5- < 10	72	26.2
≥ 10- < 15	61	22.2
≥ 15- < 20	32	11.6
≥ 20	1	0.4
Age at semen analysis, years		
≥ 18- < 26	74	26.9
≥ 26- < 36	127	46.2
≥ 36- < 56	73	26.5
≥ 56	1	0.4
Diagnosis		
Acute lymphoblastic leukemia	138	50.8
Acute myelogenous leukemia	4	1.5
CNS	16	5.8
Ewing sarcoma family of tumors	23	8.4
Hodgkin lymphoma	25	9.1
Non-Hodgkin lymphoma	15	5.5
Neuroblastoma	14	5.1
Osteosarcoma	17	6.2
Retinoblastoma	8	2.9
Rhabdomyosarcoma	7	2.6
Soft tissue sarcoma	2	0.7
Wilms tumor	5	1.8
Other	1	0.4

Abbreviation: GED, General Educational Development [test].

not complete the SJLIFE clinical evaluation, two who declined semen analysis, one who was unable to produce a semen specimen, one who had erectile dysfunction, and two who had undergone vasectomy.

Sensitivity, Specificity, and Positive and Negative Predictive Values

ROC analysis was performed to identify the optimum values of inhibin B, FSH, and the inhibin B:FSH ratio for identification of patients with azoospermia. On the basis of the learning set (Table 2), we selected the point on the ROC curve that was closest to the point (0,1) as the optimal threshold point. We also evaluated two other criteria: the minimum absolute difference between sensitivity and specificity, and the Youden index.[20] The cutoffs selected by these criteria were similar. Furthermore, the validation set provided sensitivity, specificity, and positive and negative predictive values similar to those of the learning set (Table 2). As a result, we combined the two sets and calculated sensitivity, specificity, and positive and negative predictive values by using standard methods. The results for the sensitivity, specificity, and positive and negative predictive values for the

Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Value

Variable	Inhibin B ≤ 31 ng/L	FSH > 11.5 mIU/mL	Inhibin B:FSH ratio ≤ 2.52 pg/mIU
Learning data set (n = 140)			
Sensitivity	100.0	81.0	77.1
Specificity	44.3	73.2	72.9
Positive predictive value	55.2	68.1	66.1
Negative predictive value	100.0	84.5	82.3
Validation data set (n = 135)			
Sensitivity	100.0	74.5	73.2
Specificity	45.6	75.0	76.0
Positive predictive value	48.8	61.4	61.2
Negative predictive value	100.0	84.6	84.5
Combined learning and validation data sets			
Sensitivity	100.0	78.1	75.3
Specificity	45.0	74.1	74.5
Positive predictive value	52.1	65.1	63.8
Negative predictive value	100.0	84.6	83.5

Abbreviation: FSH, follicle-stimulating hormone.

learning data set, the validation data set, and the combined data set are provided in Table 2. An inhibin B value of ≤ 31 ng/L (Fig 2A), a FSH value of more than 11.5 mIU/mL (Fig 2B), and an inhibin B:FSH ratio of ≤ 2.52 pg/mIU (Fig 2B) were determined to be the optimum levels.

The scatterplot of the serum level of inhibin B and sperm concentration is shown in Figure 3, with Spearman's correlation coefficient $rs = 0.70$. Eighty-nine of 89 azoospermic individuals (100.0%)

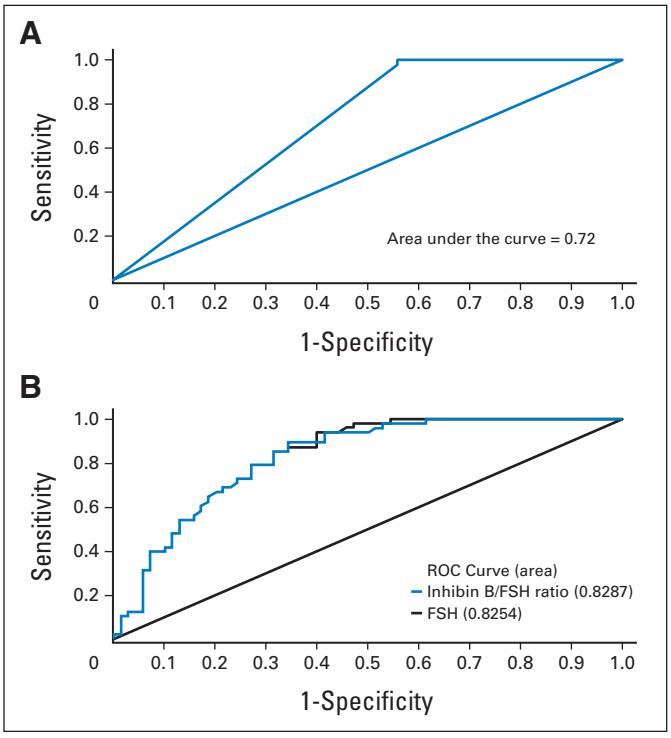

Fig 2. (A) Receiver operating characteristic (ROC) curve for inhibin B and (B) for follicle-stimulating hormone (FSH; solid line) and for inhibin B:FSH ratio (dashed line). AUC, area under the curve.

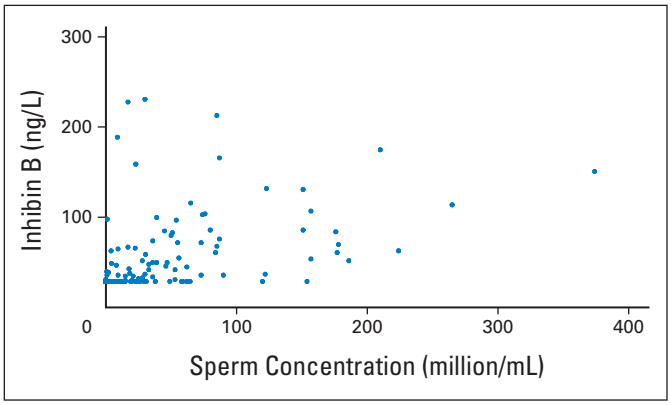

Fig 3. Scatterplot of inhibin B and sperm concentration values showing the positive relationship between these two values.

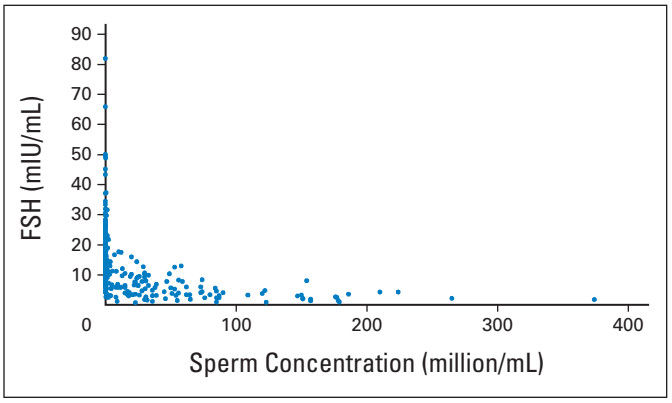

Fig 4. Scatterplot of follicle-stimulating hormone (FSH) and sperm concentration values showing the inverse relationship between these two values.

had a serum level of inhibin B ≤ 31 ng/L (Table 3). Of 149 individuals with oligospermia or a normal sperm count, 67 (45.0%) had a serum inhibin B level more than 31 ng/L. The specificity of serum inhibin B level ≤ 31 ng/L for identifying azoospermia was 45.0%, and the positive predictive value was 52.1% (Table 3).

A scatter plot of serum level of FSH and sperm concentration is shown in Figure 4 with Spearman's correlation coefficient $rs = -0.71$. Eighty-two (78.1%) of 105 azoospermic patients had a FSH level more than 11.5 mIU/mL (Table 3). One hundred twenty-six (74.1%) of those with oligospermia or a normal sperm count had a FSH level ≤ 11.5 mIU/mL. The specificity of a FSH level more than 11.5 mIU/mL for identifying azoospermia was 74.1%, and the positive predictive value was 65.1% (Table 2).

The optimal value for the inhibin B:FSH ratio for identifying participants with azoospermia was 2.52 pg/mIU. The ratio of inhibin B:FSH was not more useful for identifying participants with azoospermia than was FSH more than 11.5 mIU/mL. The specificity of the ratio ≤ 2.52 pg/mIU was 74.5%, and the positive predictive value was 63.8% (Table 2). The area under the ROC curves was 0.83 for FSH and 0.83 for the inhibin B:FSH ratio ($P = .31$; Fig 2B).

DISCUSSION

We have demonstrated that, although the serum level of inhibin B is directly and that of FSH is inversely correlated with sperm concentration, determination of the serum levels of neither inhibin B nor FSH, nor their ratio, is adequate for distinguishing between azoospermic and nonazoospermic long-term survivors of childhood cancer because of the lack of specificity and positive predictive value of both serum markers.

Table 3. Frequency of Decreased Inhibin B and Increased FSH Among Study Subjects With and Without Azoospermia

	Inhibin B (ng/L)		FSH (mIU/mL)		Inhibin B:FSH Ratio (pg/mIU)	
Characteristic	≤ 31	> 31	≤ 11.5	> 11.5	≤ 2.52	> 2.52
Azoospermia						
Yes	89	0	23	82	67	22
No	82	67	126	44	38	111

Abbreviation: FSH, follicle-stimulating hormone.

Previous investigations demonstrated a direct correlation between sperm concentration and inhibin B level in relatively small cohorts of long-term survivors of Hodgkin lymphoma treated before age 16 years (n = 21),[12] of Ewing or soft tissue sarcoma before age 22 years (n = 13),[21] and a variety of malignancies before age 16 years (n = 21 to 23).[13,22] Thomson et al[23] reported that basal inhibin B was significantly lower among azoospermic adult male survivors of childhood cancer (n = 7) than nonazoospermic adult male survivors of childhood cancer (n = 20).

Although the preceding publications demonstrated a significant correlation between the serum level of inhibin B and FSH and sperm concentration, only Romerius et al[14] previously examined the sensitivity, specificity, and positive and negative predictive values for these markers and azoospermia in survivors of childhood cancer. By using ROC analysis, they found that the optimal value for inhibin B was 50 ng/L, which was also the lower limit of the normal range for the inhibin B assay they used. When using this value, the sensitivity was 0.91 and the specificity was 0.90. The positive predictive value was 66% (95% CI, 47% to 81%), and the negative predictive value was 98% (95% CI, 93% to 100%).[14] In addition, they reported that the sensitivity of FSH for azoospermia was 0.96 and the specificity was 0.96 by using a FSH threshold of 10.9 IU/L. The positive predictive value was 50% (95% CI, 35% to 67%), and the negative predictive value was 99% (95% CI, 94% to 100%).[14]

The study by Romerius et al[14] included only 19 participants (14.7%) who had been treated with sterilizing doses and 40 (32.5%) who had been treated with nonsterilizing doses of cisplatin or alkylating agents with or without radiation therapy to cranial, supradiaphragmatic, and/or infradiaphragmatic treatment volumes and/or total-body irradiation. By contrast, all of the individuals evaluated in this study were exposed to potentially gonadotoxic treatment. In the study by Romerius et al,[14] only 23 (17.8%) of 129 participants were azoospermic compared with 105 (38.2%) of 275 in this study. The differences in the composition of the study populations, the larger number of events, and the larger size of the cohort may have contributed to the differences in specificity observed between the two studies.

We evaluated the inhibin B:FSH ratio based on the data of Andersson et al[24] who reported that an inhibin B:FSH ratio more than

23.5 ng/IU gave a sensitivity of 62% and specificity of 95% for identifying men of proven fertility in their study population. The ratio was more sensitive than either inhibin B or FSH for identifying men of proven fertility.[24] Our data suggest that the ratio is not more sensitive or specific for identification of azoospermic cancer survivors than either FSH or inhibin B. However, the limited recruitment of only 60.6% of the potentially eligible patients should be considered in the interpretation of our study findings. Notably, many of those who did not submit semen specimens had proven fertility (89 [49.7%] of 179).

Our results have important implications for counseling male long-term survivors of childhood cancer regarding their potential for fertility. Although the presence of a detectable level of inhibin B excluded azoospermia in the majority of men evaluated in this study, neither inhibin B nor FSH levels, individually or combined, should be used for advising men regarding the adequacy of spermatogenesis. All sexually active males should be instructed that, regardless of the levels of these biomarkers, adequate methods of contraception should be used if paternity is not a desired outcome of sexual activity. Moreover, because the return of spermatogenesis has been reported after prolonged periods of post-treatment azoospermia,[25-29] similar precautions should be exercised regardless of the results of a single semen analysis. Additional research is needed to identify a surrogate marker that has greater specificity and positive predictive value for sperm concentration than any of the currently available clinical biomarkers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL REPORT

Specificity of Problem-Solving Skills Training in Mothers of Children Newly Diagnosed With Cancer: Results of a Multisite Randomized Clinical Trial

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ABSTRACT

Purpose
Diagnosis of cancer in a child can be extremely stressful for parents. Bright IDEAS, a problem-solving skills training (PSST) intervention, has been shown to decrease negative affectivity (anxiety, depression, post-traumatic stress symptoms) in mothers of newly diagnosed patients. This study was designed to determine the specificity of PSST by examining its direct and indirect (eg, social support) effects compared with a nondirective support (NDS) intervention.

Patients and Methods
This randomized clinical trial included 309 English- or Spanish-speaking mothers of children diagnosed 2 to 16 weeks before recruitment. Participants completed assessments prerandomization (T1), immediately postintervention (T2), and at 3-month follow-up (T3). Both PSST and NDS consisted of eight weekly 1-hour individual sessions. Outcomes included measures of problem-solving skill and negative affectivity.

Results
There were no significant between-group differences at baseline (T1). Except for level of problem-solving skill, which was directly taught in the PSST arm, outcome measures improved equally in both groups immediately postintervention (T2). However, at the 3-month follow-up (T3), mothers in the PSST group continued to show significant improvements in mood, anxiety, and post-traumatic stress; mothers in the NDS group showed no further significant gains.

Conclusion
PSST is an effective and specific intervention whose beneficial effects continue to grow after the intervention ends. In contrast, NDS is an effective intervention while it is being administered, but its benefits plateau when active support is removed. Therefore, teaching coping skills at diagnosis has the potential to facilitate family resilience over the entire course of treatment.

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INTRODUCTION

Diagnosis and initial treatment of childhood cancer is stressful and even traumatic for parents.[1-5] They must face the life threat of the diagnosis and the many logistical demands of the patient's medical care while also managing the family's ongoing daily needs.[1,6,7] Although many parents demonstrate emotional resilience, others are at risk for developing symptoms of anxiety and depression, compromising their ability to meet these multiple demands.[2,8]

It is known that family functioning and social support are important predictors of adjustment[9-11] and that better-adjusted parents can buffer their children from the deleterious effects of stressful experiences.[12-16] For example, we previously reported that mothers of children with cancer have reduced well-being, which is directly related to the behavioral/emotional adjustment in their healthy children.[17]

Problem-solving therapy (PST),[18-20] a five-step cognitive-behavioral intervention, is used in many settings to address impaired well-being.[21-24] The intervention is designed to empower individuals to manage adverse situations by using constructive coping strategies.

The Bright IDEAS Problem-Solving Skills Training (PSST) program, which is based on PST, has been established as an effective intervention for enhancing problem-solving skills and decreasing negative affectivity (ie, anxiety, depression, post-traumatic distress) in mothers of children recently diagnosed with cancer.[25-27] Building on PST,

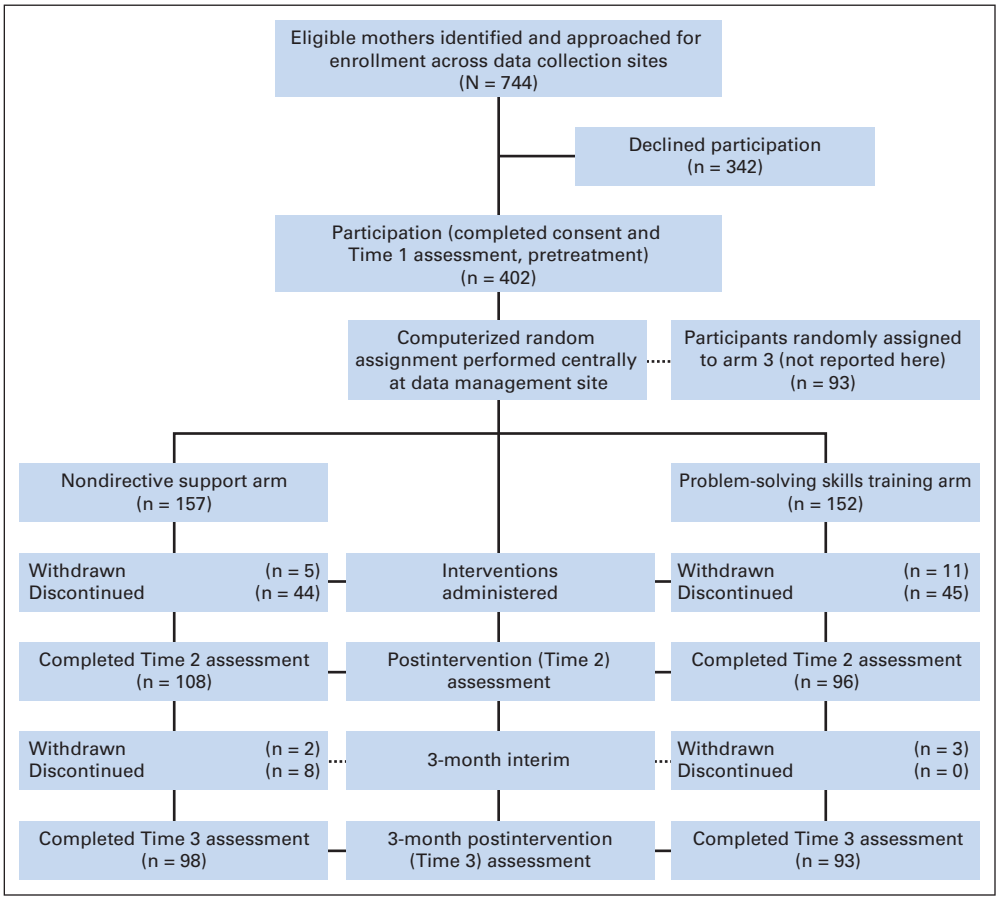

Fig 1. CONSORT diagram.

problem-solving skills training is intended for individuals who may be highly distressed but do not exhibit clinical psychopathology. Skills training also connotes a sense of personal growth.

We have conducted large-scale multi-institutional randomized clinical trials (RCTs; CONSORT diagram in Fig 1) of PSST with mothers of children recently diagnosed with cancer according to the conceptual model in Figure 2.[26,28] In these studies, PSST was compared with "usual psychosocial care" (ie, the supportive care typically provided at childhood cancer centers in the United States). We hypothesized that the primary effect of PSST would be increased problem-solving skills with a secondary effect of decreased negative affectivity. Our findings confirmed that PSST significantly decreased maternal distress and, in our mediational model, that an increase in problem-solving skills accounted for 27%, 20%, and 26% of the decrease in anxiety, depression, and post-traumatic stress symptoms, respectively. We interpreted the remaining effect as associated with other nonspecific elements of the intervention (eg, social support).[26]

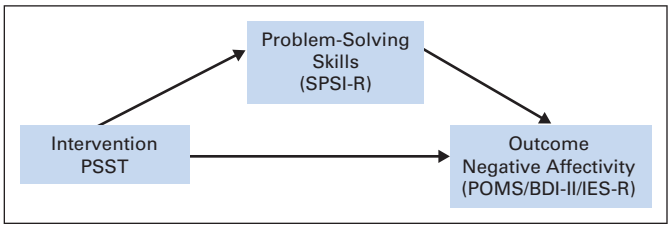

Fig 2. Conceptual model. BDI-II, Beck Depression Inventory; IES-R, Impact of Event Scale-Revised; POMS, Profile of Mood States; PSST, problem-solving skills training; SPSI-R, Social Problem-Solving Inventory-Revised.

Having demonstrated the efficacy of PSST in improving maternal well-being, we sought to examine its specificity by comparing PSST to an alternative intervention that provided similar nonspecific factors (time, attention, support, expectancy, therapeutic alliance) but did not include the specific skills-building characteristics of PSST. To accomplish this, we conducted the current RCT comparing PSST to nondirective support (NDS), a supportive psychotherapy focusing on the central activity of reflective listening, patterned after Rogers' client-centered approach.[29] NDS is often used as a comparison condition in studies of cognitive-behavioral interventions.[30,31] We chose NDS for two reasons: (1) we wished to provide mothers with a therapeutic experience structurally similar to PSST in number, length, and setting of sessions and degree of therapist support; and (2) nondirective supportive therapies are often used in populations such as ours, although efficacy is understudied. Thus, this study is a comparison of two active interventions, one of which (PSST) was designed to build problem-solving skills in addition to providing general support.

We hypothesized that, compared with mothers receiving NDS, mothers receiving PSST would demonstrate better problem-solving skills and greater reductions in negative affectivity as measured by anxiety, depression, and post-traumatic stress symptoms.

PATIENTS AND METHODS

This multi-institutional RCT was designed to investigate the efficacy of PSST relative to NDS. The original study design included a third arm consisting of PSST aided by the use of a personal digital assistant. Interim analyses indicated that this arm, although feasible, was no more effective than PSST alone and it was terminated.[25] This report focuses on the comparison of patients randomly assigned to the PSST alone (our standard intervention) and NDS arms. Note that, throughout the trial, there was an equal probability of being assigned to either PSST alone or NDS, so the exclusion of the third arm does not affect the inferences drawn from the two arms presented here.

Participants

After approval by the institutional review board at each participating site, we recruited mothers 2 to 16 weeks after their child was diagnosed with any form of cancer at four sites (University of Texas/MD Anderson Cancer Center, Children's Hospital Los Angeles, Children's Hospital Pittsburgh, and Doernbecher Pediatric Hospital). Eligibility criteria included ability to speak and read English or Spanish and residence within 50 miles of the center (to reduce transportation issues). To minimize burden, mothers were excluded if their child was in medical crisis as determined by the oncologist.

Procedures

After giving informed consent, participants completed the baseline (T1) assessment and were randomly assigned to a treatment arm by using a block design of six stratified by site and language. Participants received a modest stipend as compensation for their time.

The interventions were delivered by research assistants (RAs) who had graduate education in clinical psychology or behavioral health. Spanish-speaking RAs provided the interventions for Spanish-speaking mothers. The RAs were initially trained together as a group. Site principal investigators then provided weekly supervision to promote therapeutic excellence in intervention delivery according to the specific manual for the arm to which a participant had been randomly assigned. All sessions were digitally recorded. On a monthly basis, treatment integrity procedures tracked RA performance via structured evaluation of randomly selected sessions by reviewers blinded to study arm (see Treatment Integrity).

PSST. PSST consisted of eight 1-hour individual sessions conducted according to a comprehensive manual.[26-28] Problem solving was presented as a general coping skill applicable to a range of challenging circumstances commonly encountered during childhood cancer treatment. To promote engagement, mothers selected the particular problems to address, prompted by a list of issues often confronting parents.

To make the overall philosophy and steps of PSST easily understood, the acronym "Bright IDEAS" and a logo with a graphic of a light bulb were developed. "Bright" signifies the optimism about solving problems essential for successful implementation. The letters I (identify the problem), D (determine the options), E (evaluate options/choose the best), A (act), and S (see if it worked) signify the five essential steps of problem solving. Instructional material included a treatment manual, a pocket-size Bright IDEAS booklet, and a Bright IDEAS refrigerator magnet. (PSST materials are available through the National Cancer Institute/National Institutes of Health National Registry of Evidence-Based Programs and Practices or from the corresponding author.)

Basic therapist interpersonal techniques in PSST include active listening, reflection of feelings, clarification, and support. Delivery of the content of PSST occurred as follows: session 1: rapport building and understanding relevant personal background and medical information; session 2: introduction of PSST and the Bright IDEAS paradigm; sessions 3 to 7: review of the mother's identified problems and promotion of problem-solving strategies and skill; session 8: review of PSST, identification of relapse prevention strategies (eg, persistence, learned optimism), and termination.

NDS. As in PSST, basic therapist interpersonal techniques include active listening, reflection of feelings, clarification, and support. Essential characteristics of NDS include self-reflection in a safe, nonjudgmental environment and expression and acceptance of feelings.[29] Session 1 included initial rapport building and understanding relevant personal background and medical information, and Session 8 included termination. Throughout all eight NDS sessions, the RA maintained focus on active listening and reflecting feelings. This approach is well suited to the initial phases of crisis intervention and can be used with people from diverse backgrounds.[29]

Both PSST and NDS were delivered by the same RAs to minimize confounding elements in a therapeutic relationship such as friendliness or nonspecific social skills. A detailed treatment manual was developed for NDS similar to that for PSST. The major element distinguishing the two interventions was use or avoidance of teaching problem-solving techniques during sessions. Adherence was monitored through treatment integrity review (see Treatment Integrity).

Measures

Demographic data were collected at baseline. Assessments of problem-solving skills and negative affectivity (operationalized as anxiety, depression, and post-traumatic stress symptoms) were completed at T1 (prerandomization), T2 (immediately postintervention), and T3 (three months postintervention). Expectancy and credibility scales were completed after sessions 1 and 4 of the interventions. To maximize the reliability of our intent-to-treat analyses (see Data Analysis), all participants, except those who withdrew because of their child's medical condition, were asked to complete all assessments whether or not they completed the intervention.

Demographics

Demographic information for children included age, diagnosis, and date of diagnosis and for mothers, it included age, marital status, educational level, and self-reported race/ethnicity.

Problem-Solving Skills

The Social Problem-Solving Inventory-Revised (SPSI-R),[32,33] a 52-item self-report, linked to a multidimensional model of social problem-solving has strong reliability and validity estimates.

Negative Affectivity

The Profile of Mood States (POMS) Scale[34] is a 65-item self-report of mood with excellent reliability and validity. We used the composite total mood disturbance (TMD) scale as the outcome. The Beck Depression Inventory (BDI-II),[35] a 21-item self-report assessing depressive symptoms, is widely used for clinical and research purposes. Internal consistency ranges from 0.73 to 0.92, with good test-retest reliabilities. The Impact of Event Scale-Revised (IES-R),[36] a 22-item self-report, assesses post-traumatic stress symptoms in response to a specific event (ie, child's diagnosis with cancer). Reliability and validity are well established.

Credibility and Expectancy

To assess expectations, patients rated the intervention to which they were assigned (PSST or NDS) on credibility (by using a three-item, nine-point credibility scale) and expectancy for improvement (0% to 100% scale) after sessions 1 and 4.

Treatment Integrity

All sessions were digitally recorded and uploaded to a central secure password-protected server. Ten percent of the recordings were randomly flagged for review of process and content by one of three senior investigators on the treatment integrity team. Each had been trained in PSST, had served as a site principal investigator in previous studies, and had been a primary developer of the NDS intervention. The reviewers were blinded to treatment condition. Reviews were conducted by using a structured assessment tool based on the respective manual. In both interventions, sessions were scored on the quality of the therapeutic alliance, supportive interaction, empathy, and being nonjudgmental. In the PSST condition, reviewers rated evidence of discussion of Bright IDEAS, explanation and review of PSST worksheets, and attention to homework or between-session use of problem-solving skills. In the NDS condition, reviewers looked for promotion of self-reflection and nondirective support and, crucially, the absence of discussion of PSST. Interrater reliability was determined at the beginning of the study and tested periodically. Compliance with these criteria was more than 95% in both arms.

Data Analysis

Data analyses were generated by using the SAS System for Windows v.9.2 (2006; SAS Institute, Cary, NC). Data from all participants were included by

using an intent-to-treat approach. Longitudinal analyses were performed by using a repeated measures model for incomplete data with an unstructured covariance (SAS Proc Mixed). Time was included as an indicator variable in the two postintervention assessments. Note that a pooled estimate at T1, consistent with randomization, was used to increase precision in measuring changes. Child age and maternal age, education, marital status (single *v* other), and language were included as covariates. The trial was designed to have 89% to 98% power (depending on correlations over time) to detect differences of 0.3 standard deviations. Observed accrual and follow-up reduced power to 54% to 76%. No adjustments were made for multiple comparisons.

RESULTS

As shown in Figure 1, of the 744 eligible mothers, 402 consented to participate: 152 mothers were randomly assigned to the PSST arm and 157 were assigned to the NDS arm. Participants and nonparticipants did not differ in age ($P = .42$), primary language ($P = .19$), their child's age ($P = .25$), child's diagnosis ($P = .32$), or time since diagnosis ($P = .13$). Eleven PSST mothers and five NDS mothers withdrew because of their child's medical crisis.

Eighty-eight PSST mothers (58%) and 97 NDS mothers (62%) completed at least six sessions; the primary reason for not completing eight sessions was inability to schedule sessions within the 16-week window allowed. In all, 96 PSST mothers (63%) and 108 NDS mothers (69%) completed the postintervention (T2) assessment. Of those who completed the T2 assessment, 93 PSST mothers (97%) and 98 NDS mothers (91%) also completed the follow-up (T3) assessment. The primary reason for missing assessments was active or passive refusal (69%). Missing assessments were not associated with maternal or child demographics/baseline measures.

Table 1. Demographic Characteristics of Study Participants

Variable	PSST (n = 152) No.	PSST (n = 152) %	NDS (n = 157) No.	NDS (n = 157) %
Mother				
Age, years (mean ± SD)	36.3 ± 8.1		38.3 ± 8.3	
Race/ethnicity				
Hispanic	70	45.5	65	41.1
Non-Hispanic	82	54.5	92	58.9
White	61	40.3	72	46.2
Black	10	7.1	12	7.6
Other	11	7.1	8	5.1
Language				
English	104	68.2	109	69.6
Spanish	48	31.8	48	30.4
Highest grade in school (mean ± SD)	12.2 ± 3.9		12.9 ± 4.2	
Child				
Age, years (mean ± SD)	8.2 ± 5.7		9.4 ± 6.0	
Sex				
Male	77	50.6	88	56.3
Female	75	49.4	69	43.7
Diagnosis				
Leukemia	77	50.0	65	41.8
Solid tumor	20	13.0	25	16.5
Brain tumor	17	10.8	19	12.3
Other	38	24.7	48	31.0

Abbreviations: NDS, nondirective support; PSST, problem-solving skills training; SD, standard deviation.

Table 2. Estimated Outcome Measure Scores at T1, T2, and T3 by Intervention Group

Characteristic	Time	Group	Mean	SE	SD
SPSI-R, total score	T1	Pooled	13.3	0.15	2.65
	T2	NDS	13.7	0.21	2.69
		PSST	14.4	0.22	
	T3	NDS	14.0	0.21	2.64
		PSST	14.6	0.22	
POMS-TMD	T1	Pooled	55.7	2.36	1.26
	T2	NDS	38.3	3.50	1.54
		PSST	33.6	3.66	
	T3	NDS	35.5	3.22	1.53
		PSST	24.2	3.28	
BDI-SQRT	T1	Pooled	3.94	0.07	1.26
	T2	NDS	3.27	0.13	1.54
		PSST	3.25	0.13	
	T3	NDS	3.13	0.13	1.53
		PSST	2.71	0.13	
IES-R, total score	T1	Pooled	35.5	1.07	18.8
	T2	NDS	29.7	1.54	18.7
		PSST	28.2	1.62	
	T3	NDS	27.4	1.50	17.2
		PSST	24.2	1.53	

Abbreviations: BDI-SQRT, Beck Depression Inventory-Square Root Transformation; IES-R, Impact of Event Scale-Revised; NDS, nondirective support; POMS-TMD, Profile of Mood States-Total Mood Disturbance; PSST, problem-solving skills training; SD, standard deviation; SPSI-R, Social Problem-Solving Inventory-Revised; T1, prerandomization; T2, immediately postintervention; T3, at 3-month follow-up.

There were no between-group differences in demographics or baseline scores on assessment measures (Table 1). The distribution of diagnoses was typical of childhood cancer in the United States. Credibility and expectancy scores were not significantly different in the two groups, with mothers feeling equally positive about the potential benefit of the intervention to which she had been randomly assigned. The overall participation period for each patient averaged approximately 7 months. Table 2 lists the estimated outcome scores over time.

Table 3 indicates that, at T2, significant improvement in problem solving occurred only in the PSST group, but improvements in the

Table 3. Within-Group Changes in Outcome Measures by Intervention

Outcome	Desired Direction	Intervention	T2-T1	*P*	T3-T2	*P*
SPSI-R, total score	Positive	PSST	1.03	< .001	0.27	N/S
		NDS	0.36	.046	0.33	.05
POMS-TMD	Negative	PSST	−22.1	< .001	−9.33	< .009
		NDS	−17.4	< .001	−2.78	N/S
BDI-SQRT	Negative	PSST	−0.69	< .001	−0.54	< .001
		NDS	−0.67	< .001	−0.14	N/S
IES-R, total score	Negative	PSST	−7.30	< .001	−4.01	.012
		NDS	−5.81	< .001	−2.27	N/S

Abbreviations: BDI-SQRT, Beck Depression Inventory-Square Root Transformation; IES-R, Impact of Event Scale-Revised; NDS, nondirective support; N/S, not significant; POMS-TMD, Profile of Mood States-Total Mood Disturbance; PSST, problem-solving skills training; SPSI-R, Social Problem-Solving Inventory-Revised; T1, prerandomization; T2, immediately postintervention; T3, at 3-month follow-up.

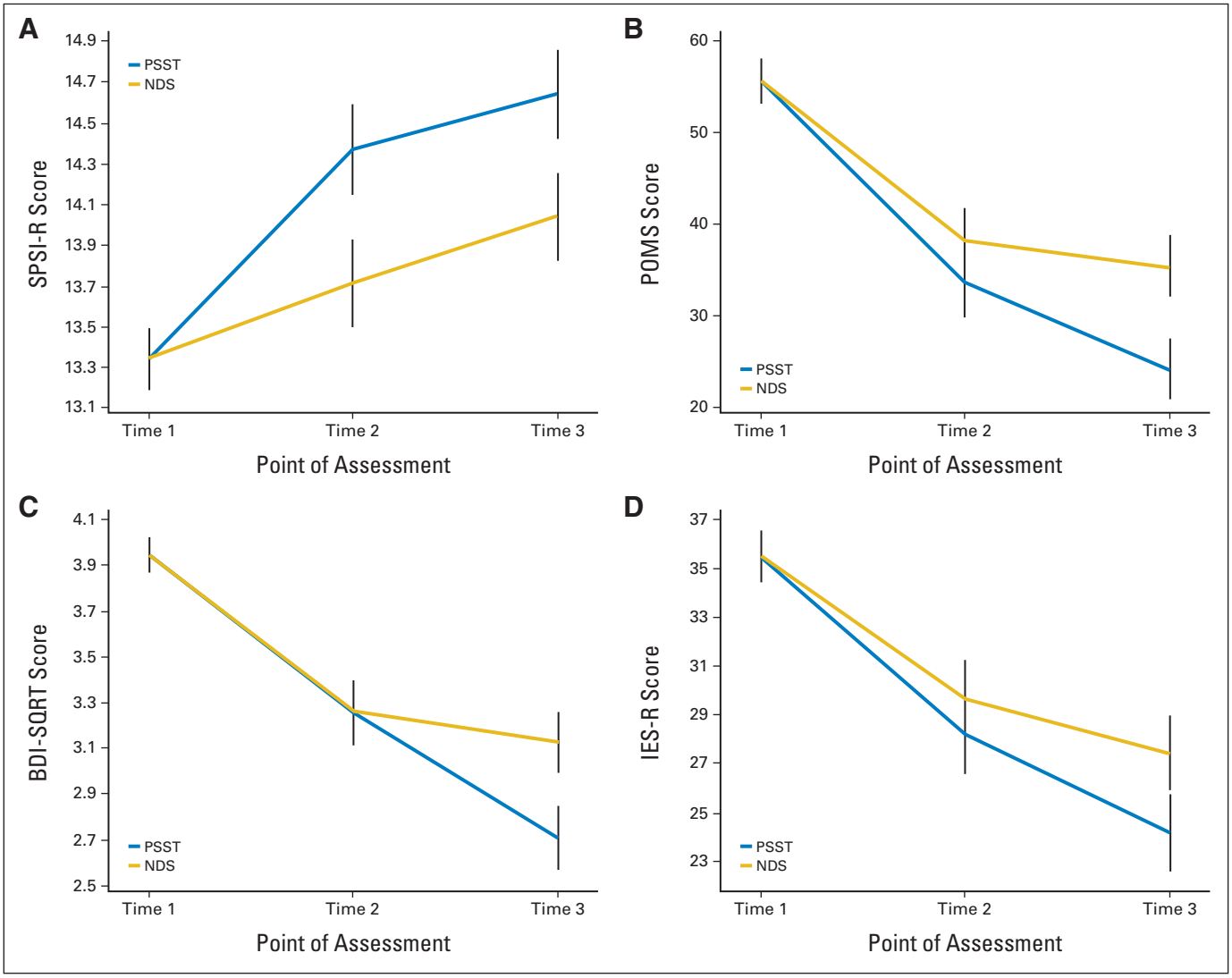

Fig 3. Estimated outcome measure scores at T1 (prerandomization), T2 (immediately postintervention), and T3 (3-month follow-up). Mean + SE (vertical lines). BDI-SQRT, Beck Depression Inventory-Square Root Transformation; IES-R, Impact of Event Scale-Revised; NDS, nondirective support; POMS, Profile of Mood States; PSST, problem-solving skills training; SPSI-R, Social Problem-Solving Inventory-Revised.

three dimensions of negative affectivity occurred in mothers in both conditions, although the changes were slightly greater in the PSST group. Although there continued to be significant improvements in negative affectivity in the PSST group from T2 to T3, only minor improvements were found among the NDS group (Fig 3).

Table 4 lists the between-group differences in outcome. Again, with the exception of the SPSI-R, mothers in the two conditions demonstrated equivalent therapeutic gains in negative affectivity from T1 to T2. However, at T3, the PSST condition proved superior, because continued improvements occurred in that group at a significantly greater rate.

DISCUSSION

The major aim of this RCT was to examine the specificity of PSST in reducing distress in mothers of children recently diagnosed with cancer. For comparison, we developed an active nonspecific behavioral intervention, NDS, which provided the same time and attention from RAs and focused on nonjudgmental support and expression of feelings. Although virtually identical interpersonal elements were present in both conditions, NDS had none of the specific problem-solving

Table 4. Differences in Outcome Measures, PSST-NDS

Outcome	Desired Direction	T2	*P*	T3	*P*
SPSI-R, total score	Positive	0.66	.011	0.60	.023
POMS-TMD	Negative	−4.70	N/S	−11.2	.010
BDI-SQRT	Negative	−0.02	N/S	−0.42	.016
IES-R, total score	Negative	−1.49	N/S	−3.24	.104

Abbreviations: BDI-SQRT, Beck Depression Inventory-Square Root Transformation; IES-R, Impact of Event Scale-Revised; NDS, nondirective support; N/S, not significant; POMS-TMD, Profile of Mood States-Total Mood Disturbance; PSST, problem-solving skills training; SPSI-R, Social Problem-Solving Inventory-Revised; T2, immediately postintervention; T3, at 3-month follow-up.

elements of PSST, allowing us to measure the specific effects of training mothers in the use of this skill.

We found that, immediately following the intervention (T2), problem-solving skills were significantly higher in the PSST group, as expected, because these skills were specifically taught in PSST. However, there were no significant between-group differences in POMS, BDI-II, or IES-R scores, although improvements were slightly larger for the PSST group. Remarkably, at 3-month follow-up (T3), mothers in the PSST group had continued to improve after treatment cessation (T2), resulting in significant between-group differences (Table 4; Fig 3). Thus, it appears that having a caring person who provides empathic, nondirective support is, indeed, beneficial to the mother's well-being, but the effect is limited to the time that support is actually provided. In contrast, provision of problem-solving skills training allows for sustained and increasing positive effects, presumably a result of teaching coping skills.

We believe this is the first RTC to examine the benefits of a purely supportive intervention (NDS) with mothers of newly diagnosed children with cancer, despite its wide use in this population. Although this study did not have a no-treatment or usual care comparison group, the immediate effects of NDS appear superior to no treatment, as indicated by our previous findings of significant differences between PSST and usual care at T2.[26] However, findings of this study indicate that the effects of NDS seem to plateau when the intervention ends.

Our assessment completion rates of 61% for PSST mothers and 63% for NDS mothers were lower than anticipated from previous work. This may be due, in part, to the fact that all participants were engaged in an intervention. In our experience, the possibility of being randomly assigned to usual care (with minimal commitment) may actually be an inducement to enrollment. However, our results are not atypical of the field, reflecting the reality that recruiting and retaining participants in psychosocial oncology research is difficult.[37]

Another limitation is inclusion of mothers only. Engaging fathers is challenging because of limited accessibility. Many parents are compelled to divide family responsibilities. Fathers often serve as primary wage earners, securing health benefits, as well as the main caregivers for siblings, especially during hospitalization. We recognize that fathers experience distress when their child is diagnosed and could profit from intervention. We must find ways to include them in future projects.

Follow-up was limited to 3 months. Six to 12 months would allow more time to explore the durability of PSST. The benefits of a longer study, however, in which retention may be problematic, must be balanced against a briefer follow-up such as ours with an exceptionally good retention rate of more than 90% between T2 and T3.

Despite these limitations, we remain confident of our findings for several reasons. (1) We had equal participation by mothers in both groups. (2) Intent-to-treat analysis included all enrollees who completed T1 regardless of participation (even zero), reflecting the most conservative estimates of effect. (3) More than 90% of mothers in both groups who completed T2 also completed T3. Thus, changes from T2 to T3, both within and between groups, represent data from the vast majority of patients, maximizing the stability of our findings.

RCTs are critical to identifying the active elements of an intervention. Our findings show that PSST has significant potency beyond the supportive elements and factors such as time and attention that characterize NDS, and these effects continue to manifest after PSST ends. However, our findings clearly support the need for longer follow-up to investigate the durability of these new skills and their effect on distress over time.

We strongly endorse including fathers and other caregivers and believe the simple steps of the Bright IDEAS paradigm are applicable to problems encountered across many illness types and situations. However, face-to-face PSST is labor intensive. Increased computer accessibility, social networking, and online training are likely key to broad dissemination especially because, once designed and implemented, the cost of an online intervention/participant decreases as usage increases. On the basis of experience with a computer-based intelligent agent[38,39] and PDA-enhanced PSST,[25] development and validation of an effective Internet version of PSST as an alternative to face-to-face training will make PSST a highly accessible intervention, especially at centers with limited behavioral health services. Bright IDEAS has been designated as a research-tested intervention program and is included in the National Registry of Evidence-Based Programs and Practices.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Collection and assembly of data: Diane L. Fairclough, Martha A. Askins, Ernest R. Katz, Robert B. Noll, Robert W. Butler
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Final approval of manuscript: All authors

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ORIGINAL REPORT

Implementation of Universal Microsatellite Instability and Immunohistochemistry Screening for Diagnosing Lynch Syndrome in a Large Academic Medical Center

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ABSTRACT

Purpose
In 2009, the Evaluation of Genomic Applications in Practice and Prevention recommended that all colorectal cancers (CRCs) be screened for Lynch syndrome (LS) through microsatellite instability (MSI) or immunohistochemistry (IHC). No studies report how this process is implemented on a health system–wide basis.

Methods
Since 2004, Cleveland Clinic has screened CRC specimens with MSI/IHC. Between January 2004 and July 2007, MSI/IHC results went only to the colorectal surgeon (approach 1). Between August 2007 and June 2008, colorectal surgeons and a genetic counselor received the MSI/IHC results, and the counselor e-mailed the colorectal surgeon regarding appropriate patients for genetic counseling (GC) referral (approach 2). After July 2008, the colorectal surgeon and counselor received MSI/IHC results, but the counselor contacted the patient to facilitate referral (approach 3). In approaches 2 and 3, patients were presumed to have sporadic CRC if the tumor lacked MLH1 expression and was also *BRAF* mutated or if the patient was diagnosed at age greater than 72 years and had no cancer family history.

Results
Abnormal MSI/IHC results occurred in 178 (16%) of 1,108 patients. In approach 1, 21 (55%) of 38 patients with abnormal MSI/IHC were referred for GC, 12 (32%) of 38 underwent GC, and 10 (26%) of 38 underwent genetic testing (GT). In approach 2, nine (82%) of 11 patients were referred for GC, seven (64%) of 11 underwent GC, and five (45%) of 11 underwent GT. In approach 3, 56 (100%) of 56 patients were referred for GC, 40 (71%) of 56 underwent GC, and 37 (66%) of 56 underwent GT. Time from referral to GC was 10-fold quicker in approach 3 than approach 1.

Conclusion
Implementation of universal MSI/IHC with GC/GT, along with effective multidisciplinary communication and plans of responsibility for patient contact, resulted in increased identification of patients with LS.

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INTRODUCTION

Lynch syndrome (LS) is the most common hereditary colorectal cancer (CRC) syndrome, affecting one in 35 patients with CRC.[1] It is an autosomal dominant condition caused by gene alterations in the mismatch repair pathway (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*). LS is associated with an increased risk of colorectal, endometrial, gastric, ovarian, small bowel, hepatobiliary, urothelial, and other cancers. Identification of these patients is critical to offer increased cancer surveillance and prophylactic surgeries to reduce the risk of cancer in the patients as well as their relatives. This has been underscored as one of the agenda items in Healthy People 2020.[2]

Traditionally, patients at risk for LS were determined by clinical criteria such as the Amsterdam Criteria[3] or the Bethesda Guidelines.[4] The Amsterdam Criteria rely on clinicians to obtain a detailed family history and have been shown to have a sensitivity of less than 50%.[1,5] Although the sensitivity of the Bethesda Guidelines is greater than 72%, these guidelines are burdensome to recall and have been shown to be poorly implemented in clinical practice.[1,6]

In 2009, the Evaluation of Genomic Applications in Practice and Prevention recommended all

newly diagnosed patients with CRC be screened for LS through polymerase chain reaction–based microsatellite instability (MSI) testing or immunohistochemistry (IHC).[7] Although universal screening of patients with CRC is conceptually possible, the development and implementation of systematic screening are complicated. These programs require cooperation and effective communication across multiple disciplines to ensure that patients at risk of LS are appropriately identified, notified of abnormal results, and referred for genetic counseling (GC) and genetic testing (GT). Here, we report our experience at a large academic medical center with a complex health system using three approaches to our institutional screening program with an aim to compare a more active approach to passive approaches to LS screening.

METHODS

Setting

The Cleveland Clinic is a large academic medical center with a complex health system comprising an academic practice on the main campus, two regional community hospitals, and multiple family health centers across northeast Ohio. Pathology, headquartered on the main campus, performs all histopathology, including polymerase chain reaction–based MSI analysis and IHC for mismatch repair proteins. Since September 2010, the western regional community hospital submitted all CRCs to Cleveland Clinic's Department of Anatomic Pathology. The department only started performing MSI/IHC on some CRCs for the eastern regional community hospital in January 2009 and all CRCs from the western regional hospital in September 2010. Therefore, for purposes of this study, only CRCs surgically resected on the main campus were included for analysis.

MSI and IHC

Since 2004, the Cleveland Clinic screened CRCs with MSI and/or IHC. Results were kept in a registry approved by the Cleveland Clinic Institutional Review Board. Between January 2004 and March 2009, MSI testing was performed on all primary, surgically resected CRCs in patients diagnosed at age less than 50 years, that were right-sided or displayed any MSI-high (MSI-H) histology, as previously described.[8] Any tumor that was MSI-low or MSI-H then underwent IHC. In April 2009, a universal screening approach was implemented, and all resected CRCs were screened either by MSI testing or IHC. Starting in June 2010, *BRAF* testing was automatically performed on any MSI-H tumor that showed lack of expression of MLH1.

Results Disclosure

Between January 2004 and July 2007, MSI/IHC results went only to the colorectal surgeon a few weeks after the initial pathology report was signed out via an addendum to the surgical pathology report in the electronic medical record. Disclosure of results and referral to GC occurred at the discretion of the colorectal surgeon (approach 1). Between August 2007 and June 2008, the colorectal surgeon received the results via the electronic medical record, but the Department of Anatomic Pathology also e-mailed a weekly report of all MSI/IHC cases to the genetic counselor, as agreed on by the providers in pathology, colorectal surgery, and clinical cancer genetics. The genetic counselor then e-mailed the colorectal surgeon regarding which patients were appropriate for a GC referral; however, it was the surgeon's responsibility to notify patients of their results and make the referral (approach 2). Between July 2008 and January 2012, the colorectal surgeon and genetic counselor received results as outlined in approach 2, but the counselor contacted the patient directly via telephone and/or letter on behalf of the surgeon to notify the patient of the results and facilitate a GC referral (approach 3).

In approaches 2 and 3, the genetic counselor reviewed all patients with lack of expression of MLH1 to determine which patients were most likely to have LS and, thus, were most appropriate for GC. Patients were presumed to have sporadic CRC and were not recommended for GC if the cancer was diagnosed at age $\geq$ 72 years (median age of CRC in the general population per 2008 Surveillance, Epidemiology, and End Results data) and there was no documented family history of cancer. After the addition of *BRAF* testing, none of the 24 patients with the V600E mutation were recommended for referral. All patients with lack of expression of MSH2, MSH6, or PMS2 were considered appropriate for GC referral.

Statistics

Descriptive statistics were used for each approach. Significant end points were GC referral, GC, and germline GT. Two-tailed *P* values were calculated using χ^2 with Yates correction for number of patients referred for GC, patients who underwent GC and germline GT, and patients identified to have a deleterious mutation between approaches 1 and 2, 2 and 3, and 1 and 3. Values for each approach were calculated based on the number of patients who should have been referred for GC. Mean, median, and standard deviation were calculated for the time from GC referral to GC appointment for each approach. Unpaired *t* tests were used to make comparisons between approaches 1 and 2, 2 and 3, and 1 and 3 for the time between GC referral and GC appointment.

RESULTS

Over an 8-year period, abnormal screening results occurred in 178 (16%) of 1,108 patients (Table 1, Fig 1). In approaches 2 and 3, 59 (33%) of 178 CRCs were presumed sporadic (Fig 1), by the operational definition noted earlier in Methods. Retrospective review of patients screened during approach 1 revealed that 38 patients should have been referred for GC, instead of the 21 (57%) who were actually referred (Fig 1). When compared with approach 1, a significantly greater proportion of patients were referred to GC in approaches 2 ($P = .0232$) and 3 ($P < .001$, Fig 1).

GC

When compared with approach 1, significantly more patients underwent GC in approach 3 ($P < .001$) Discrepancies were noted between the number of patients referred to GC and the number who pursued GC (Fig 1, Table 2). The primary reason for declined visits

Table 1. Summary of Abnormal MSI and IHC Results for Each Approach

	Approach 1		Approach 2		Approach 3	
Result	No. of Patients	%	No. of Patients	%	No. of Patients	%
MSI-low/high, IHC NOS	6	11.5	0	0	1	0.1
MLH1/PMS2 loss	37	71.2	14	82.3	88	80.7
MSH2/MSH6 loss	7	13.5	2	11.8	11	10.0
MSH6 loss	2	3.8	1	5.9	6	5.5
PMS2 loss	0	0	0	0	3	2.8

Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability; NOS, not otherwise specified.

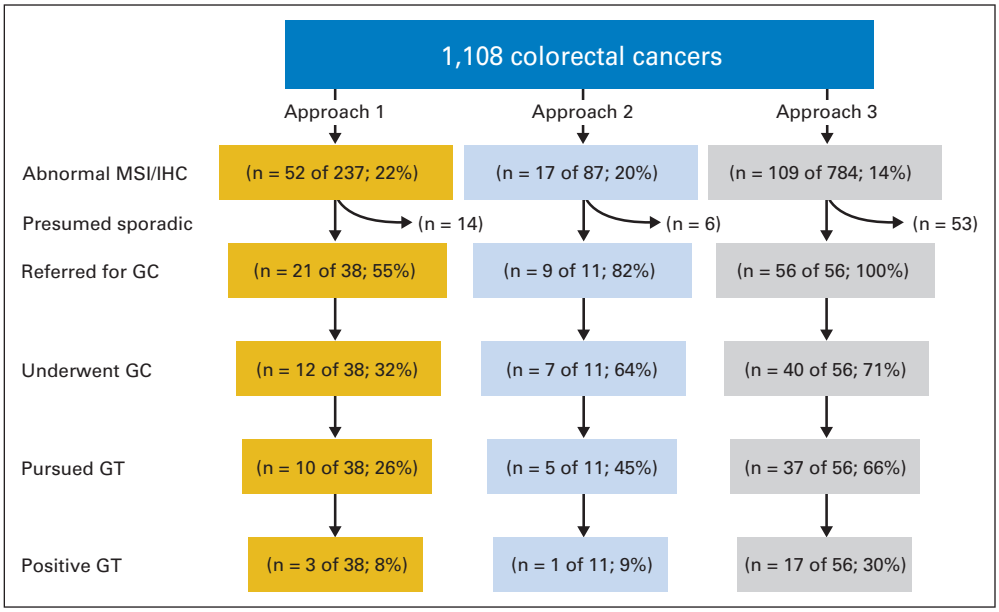

Fig 1. Schema summarizing the three approaches for microsatellite instability (MSI)/immunohistochemistry (IHC) screening for Lynch syndrome. A summary of screen-abnormal results for each approach is shown, as well as the number of patients who were referred, who pursued genetic counseling (GC) and genetic testing (GT), and who were found to have deleterious mutations.

was that patients felt GC would not benefit themselves or their family members.

Detailed, three- to four-generation pedigrees were obtained from all patients who pursued GC. Only 12 (20.3%) of 59 patients satisfied the Amsterdam Criteria. A higher percentage of patients met the Revised Bethesda Guidelines (39 of 59 patients, 66.1%), but these data are skewed because our initial testing criteria were loosely based on the Bethesda Guidelines.

Across all approaches, variation was observed in the time between referral and GC appointment (Table 3). Overall, the median number of days between referral and GC was 13 days. Six patients were seen more than 1 year after the referral was made. When compared with approach 1, patients referred during approach 3 were seen for GC significantly sooner ($P < .001$).

GT

Fifty-two (88%) of 59 patients who pursed GC proceeded with GT. Compared with approach 1, more patients had germline testing in approach 3 ($P < .001$) and more deleterious mutations were identified ($P = .0185$). Three patients declined testing, two patients never had blood drawn, one patient never received consent from the medical power of attorney, and one patient canceled because of lack of insurance coverage. Overall, we identified 21 deleterious mutations (*MLH1*, n = 9; *MSH2*, n = 10; *MSH6*, n = 2). Six patients with variants of uncertain significance were identified (*MLH1*, n = 2; *MSH2*, n = 3; *MSH6*, n = 1), two patients had sporadic CRC (one *BRAF* and one *MLH1* promoter hypermethylation), and the remaining 23 patients had uninformative GT results.

Table 2. Reasons Why Genetic Counseling Was Not Pursued After Referral

Reason	No. of Patients	%
Lost to follow-up	12	44.4
Declined visit	11	40.7
Death	2	7.4
No show	2	7.4

DISCUSSION

There is strong support in the literature to develop universal screening for LS among all newly diagnosed patients with CRC. It has been shown that universal screening is feasible[9] and also cost effective.[10,11] Furthermore, chain-of-evidence methodology has shown this could lead to improved clinical outcomes for patients and their families.[7] However, the success of universal screening is dependent on patients receiving the screening results with subsequent pursuit of GC and germline GT.

Our current study clearly showed a higher detection rate of LS by approach 3 ($P = .0185$; three patients in the period of 42 months from January 2004 to July 2007 by approach 1, one patient in the period of 10 months from August 2007 to June 2008 by approach 2, and 17 patients in the period of 42 months from July 2008 to January 2012 by approach 3) even as the monthly surgically resected CRC number remained reasonably stable. Of the patients for whom we had detailed pedigrees, we found that only 20.3% of patients met Amsterdam Criteria and 66.1% met Bethesda Guidelines. The increased LS diagnostic rate is likely a result of a combination of universal LS screening in all surgically resected CRCs and

Table 3. Average Length of Time Between Referral and Genetic Counseling for Each Approach

Time Between Referral and Counseling	No. of Days		
	Approach 1	Approach 2	Approach 3
Average time	457	293	44
Median time	156	30	9
Standard deviation	717	522	93
Range	0-1,945	6-1,218	0-365

the development of an active approach of reporting abnormal MSI/IHC screening results to patients.

The initial approach, approach 1, used what is standard in returning results from anatomic pathology practice (ie, with an addendum in the pathology report). In theory, this addendum should trigger the surgeon-of-record to act, by calling the patient in question and suggesting a GC referral. Unfortunately, this assumption, especially in a large academic medical center, may result in genetics professionals, gastroenterologists, colorectal surgeons, and pathologists operating in silos, which, at our center, yielded only half of appropriate patients being referred. Sanchez et al[12] previously published that when departments operate independently, an inappropriately low number of patients at risk of LS are referred for diagnostic testing. Recognizing the potential impact of this limited practice on our patients, changes were made to improve the process. A more collaborative approach evolved, resulting in interdisciplinary communication and clear roles for each subspecialist, which resulted in all patients being referred for counseling. As the data highlight, this evolution occurred over years and required tremendous commitment and buy-in from the numerous health care professionals. Unfortunately, barriers still remain to getting patients to undergo GC.

The challenge of capturing all patients in a screening program is not unique to the Cleveland Clinic Health System. Backes et al[13] recently reported poor compliance with GC referral among patients with IHC results suggestive of LS. They found that only 27 (57%) of 47 patients expected to benefit from GC were referred and only 13 (28%) of 47 patients pursued GC. This group also surveyed patients about barriers to pursuing GC services and their risk perception. The most frequently quoted barrier was insurance coverage/cost, and they found that most patients underestimated their risk of LS and associated cancers.

Like Backes et al,[13] we found that there were barriers to capturing patients for GC who were referred across all approaches. The most common reason for patients not pursuing GC at our center was that they were lost to follow-up. As with other large, tertiary-care hospitals, the Cleveland Clinic sees patients who undergo surgery but continue care at a referring (usually local) center. This complicates contacting patients to discuss results and facilitation of a GC referral. In all of these cases across all three approaches, we attempted to contact patients by telephone and/or letter to discuss the results and offered referral to a local genetic counselor, but we have yet to receive any follow-up.

In addition to the patients lost to follow-up, there were 11 patients who declined GC. The most common reason for not proceeding to GC was a perceived lack of benefit to the patient and/or his or her family, highlighting a clear educational need for this population. As suggested by Chubak et al,[14] an informational fact sheet could be provided in the patient's preoperative materials to increase awareness about MSI/IHC testing and LS. Additionally, managing physicians have a key role in educating and encouraging patients who are initial decliners to using GC services.

Finally, two patients died before the completion of MSI/IHC results. Both patients' IHC results suggest that they had LS (one lacked MSH2/MSH6 and the other lacked MSH6). Given that there could be risk to other family members, it was important to communicate these results to the next of kin or medical power of attorney. Again, despite our attempts, we have had no success communicating with the deceased's family.

It is also important that patients undergo GC in a timely manner, so that, if indicated, patients can receive increased cancer surveillance. There was wide variability in the time between referral and GC (range, same day to 5 years). The shortest interval occurred in approach 3. This coincided with a genetic counselor providing care in colorectal surgery clinics. When possible, patients were offered a GC visit after their postoperative appointment to eliminate barriers associated with scheduling another appointment on a separate day. We believe that access to genetic care is a key factor in successful uptake of GC for those who screen positive.

The strength of this study is that it is the first of its kind to provide a framework for practical clinical implementation of universal MSI/IHC testing. The major limitation of this study is that it was performed at a single academic medical center, albeit large and complex. However, although a variety of approaches could be used for reporting abnormal results and referring patients for GC, all programs will face similar challenges.

It is possible to have a successful program with a high uptake of diagnostic, genetic services. Before initiating universal screening, a plan should be developed in accordance with institution-specific policies. To achieve the greatest success, the program minimally must have representation from colorectal surgery, gastroenterology, gynecologists, pathology, and genetics. Over the duration of our program, we have also sought input from our bioethicists and oncologists. Most importantly, a plan should be developed to assign roles and responsibility for screen results reporting to the patients and facilitating GC referral. At our institution, the screen results are reported to the patients by a genetic counselor, but this could be handled by a variety of disciplines as long as it is clearly detailed whose responsibility it is. The providers who follow these patients over time, such as the surgeons, oncologists, gynecologists, and gastroenterologists, play a critical role in educating and encouraging patients who were initial decliners to pursue GC. Thought should be given to how cases will be handled when patients are lost to follow-up or deceased. Finally, development of educational material based on the most updated information regarding LS screening and diagnosis is needed to increase GC compliance and GT rate in patients with newly diagnosed CRC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL REPORT

Fluorouracil, Leucovorin, and Irinotecan Plus Either Sunitinib or Placebo in Metastatic Colorectal Cancer: A Randomized, Phase III Trial

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ABSTRACT

Purpose
This double-blind, phase III study aimed to demonstrate that sunitinib plus FOLFIRI (fluorouracil, leucovorin, and irinotecan) was superior to placebo plus FOLFIRI in previously untreated metastatic colorectal cancer (mCRC).

Patients and Methods
Patients were randomly assigned to receive FOLFIRI and either sunitinib (37.5 mg per day) or placebo (4 weeks on treatment, followed by 2 weeks off [schedule 4/2]) until disease progression. The primary end point was progression-free survival (PFS). Secondary end points included overall survival, safety, and patient-reported outcomes. The correlation between genotype and clinical outcomes was also analyzed.

Results
In all, 768 patients were randomly assigned to sunitinib plus FOLFIRI (n = 386) or placebo plus FOLFIRI (n = 382). Following a second prespecified interim analysis, the study was stopped because of potential futility of sunitinib plus FOLFIRI. Final results are reported. The PFS hazard ratio was 1.095 (95% CI, 0.892 to 1.344; one-sided stratified log-rank $P = .807$), indicating a lack of superiority for sunitinib plus FOLFIRI. Median PFS for the sunitinib arm was 7.8 months (95% CI, 7.1 to 8.4 months) versus 8.4 months (95% CI, 7.6 to 9.2 months) for the placebo arm. Sunitinib plus FOLFIRI was associated with more grade ≥ 3 adverse events and laboratory abnormalities than placebo (especially diarrhea, stomatitis/oral syndromes, fatigue, hand-foot syndrome, neutropenia, thrombocytopenia, anemia, and febrile neutropenia). More deaths as a result of toxicity (12 *v* four) and significantly more dose delays, dose reductions, and treatment discontinuations occurred in the sunitinib arm.

Conclusion
Sunitinib 37.5 mg per day (schedule 4/2) plus FOLFIRI is not superior to FOLFIRI alone and has a poorer safety profile. This combination regimen is not recommended for previously untreated mCRC.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, with increasing incidence, particularly in developing countries.[1] In patients with metastatic CRC (mCRC), chemotherapy alone yields median survival durations of approximately 20 months.[2-4] Although the combination of bevacizumab and chemotherapy has modestly improved outcomes in treatment-naïve patients,[5] additional therapeutic options are needed.

Sunitinib malate (SUTENT; Pfizer, New York, NY) is an oral, multitargeted inhibitor of vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors, as well as other receptor tyrosine kinases.[6-10] Sunitinib is currently a multinationally approved drug for the treatment of advanced renal cell carcinoma, imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumor, and unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors.[11]

In preclinical CRC models, sunitinib demonstrated single-agent antitumor activity at well-tolerated doses.[6] When sunitinib was combined with irinotecan, the combination was superior compared with either single agent alone (Pfizer, data on file). A phase II study of single-agent sunitinib after failure of standard mCRC therapy found median

overall survival (OS) to be 10.2 and 7.1 months in patients with bevacizumab-untreated and bevacizumab-pretreated tumors, respectively (sunitinib treatment: 50 mg per day for 4 weeks on therapy, followed by 2 weeks off [schedule 4/2]).[12] The investigators concluded that the mechanism of action and acceptable safety profile of sunitinib warranted further exploration in combination with standard mCRC regimens.

A subsequent phase I study investigated sunitinib combined with fluorouracil, leucovorin, and irinotecan (FOLFIRI) in treatment-naïve patients with mCRC and determined that the maximum-tolerated dose of sunitinib was 37.5 mg per day administered on schedule 4/2.[13] This regimen showed promising antitumor activity and was further evaluated in a double-blind, randomized phase III study. This trial was initiated in July 2007 to determine whether sunitinib plus FOLFIRI was superior to placebo plus FOLFIRI in prolonging progression-free survival (PFS) in the first-line treatment of patients with mCRC. The study was stopped in June 2009 at the recommendation of an independent data monitoring committee following a second prespecified interim analysis because of potential futility of the combination regimen. Final results are reported here.

PATIENTS AND METHODS

Study Population

Patients were age ≥ 18 years, had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and adequate organ function, and had histologically or cytologically confirmed colorectal adenocarcinoma with metastatic disease documented by diagnostic imaging. All patients had previously untreated metastatic disease not amenable to surgery (although adjuvant therapy for primary CRC was permitted provided that ≥ 6 months had elapsed from the conclusion of adjuvant therapy to the documentation of recurrent disease), were candidates for FOLFIRI therapy, and had one or more measurable lesions based on Response Evaluation Criteria in Solid Tumors, version 1.0 (RECIST).[14]

Patients were excluded if they had prior treatment with a tyrosine kinase inhibitor, CNS involvement, or previous radiation treatment to more than 30% of bone marrow or to all measurable areas of metastatic disease. Additional exclusion criteria are listed in Materials and Methods in the Appendix (online only).

Study Design and Treatment

This randomized, double-blind, placebo-controlled phase III study was conducted in multiple centers worldwide to investigate the efficacy and safety/tolerability of sunitinib combined with FOLFIRI. The study was approved by the institutional review board or independent ethics committee of each participating center and complied with the International Conference on Harmonization Good Clinical Practice guidelines and applicable local regulatory requirements. All patients provided written informed consent.

Patients were enrolled by clinical-site staff who used a Web-based system provided by the study sponsor and were then randomly assigned 1:1 to receive FOLFIRI plus either sunitinib or placebo (Fig 1). Patients were stratified on the basis of ECOG PS (0 or 1), number of organs with metastases (one or more than one), primary tumor site (colon or rectum), and prior adjuvant treatment (yes or no).

Intravenous FOLFIRI was administered in the standard fashion every 2 weeks: irinotecan 180 mg/m^2, levo-leucovorin 200 mg/m^2 immediately followed by fluorouracil 400 mg/m^2 bolus, and then fluorouracil 2,400 mg/m^2 as a 46-hour infusion. Oral sunitinib (37.5 mg per day) or placebo was administered on schedule 4/2.

Dose delays or reductions were permitted to manage treatment-related adverse events (AEs). For sunitinib/placebo or FOLFIRI, dose interruptions of more than 4 weeks were not permitted. Sunitinib/placebo doses could be reduced to 25 mg per day; FOLFIRI doses could be reduced according to institutional practices. The use of hematopoietic growth factors was permitted.

Treatment cycles were 6 weeks in duration (each 6-week sunitinib/placebo cycle included 3 cycles of FOLFIRI). Treatment was planned to continue until disease progression (unless unacceptable toxicity occurred or consent was withdrawn) for a maximum of 30 months. Crossover between treatment arms was not permitted.

Assessments

The primary study end point was PFS defined as time from the date of random assignment to the date of first documentation of objective tumor progression or death as a result of any cause, whichever occurred first. Secondary end points included OS, objective response rate (ORR) based on RECIST, version 1.0,[14] safety, and patient-reported outcomes. In addition, genotype analysis of biologic samples was performed, after informed consent, to investigate potential associations with efficacy or toxicity. Additional information on the patient-reported outcomes and genotype analysis components of this study can be found in the Appendix.

Tumors were imaged at baseline, every 6 weeks, or whenever disease progression was suspected to confirm an objective response (partial response or complete response) ≥ 4 weeks after initial documentation of response, at study withdrawal (if not done in the previous 6 weeks), and after study drug discontinuation. Tumor assessments were subjected to blinded central review.

Safety was evaluated by using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 and through assessment of laboratory results, physical examinations, clinical history, PS, vital signs, and ECGs. An independent data monitoring committee reviewed safety data periodically from January 2008.

Statistical Methods

Study sample size was determined based on the assumptions of a median PFS of 8.0 months for patients receiving placebo plus FOLFIRI[4] and 10.8 months for patients receiving sunitinib plus FOLFIRI (a 35% improvement). In total, 568 PFS events were required for a one-sided stratified log-rank test with a significance level of 0.025% and 85% power to detect a statistically significant difference between the treatment arms (superiority design). The number of events was determined by a group-sequential design with two interim analyses and one final analysis. The interim analyses were planned at 25% and 60% of the 568 PFS events, and the stopping boundary for futility at the second interim analysis was a hazard ratio (HR) of ≥ 0.876 based on an O'Brien-Fleming stopping boundary.[15] The planned sample size was 720 patients (360 per arm).

The efficacy analysis population included all randomly assigned patients. The safety analysis population included all patients who received at least one dose of study medication. Time-to-event end points were analyzed by using Kaplan-Meier methods. Cox regression models were used to explore potential influences of baseline and on-treatment characteristics on PFS.

RESULTS

Study Conduct, Patients, and Treatment Administration

Enrollment began in July 2007. At the second interim analysis in June 2009, after enrollment was complete and 367 PFS events had occurred, the PFS HR was 1.095 in favor of the placebo arm (95% CI, 0.892 to 1.344; one-sided stratified log-rank $P = .807$). The data monitoring committee noted that the futility boundary had been crossed and that there were increased toxic events (including neutropenia and diarrhea) in patients who received sunitinib plus FOLFIRI compared with placebo plus FOLFIRI. At this point, patients on treatment were notified and treatment was unblinded. Sunitinib discontinuation was recommended or left to investigator discretion in cases of clinical benefit. The last patient visit occurred in March 2010.

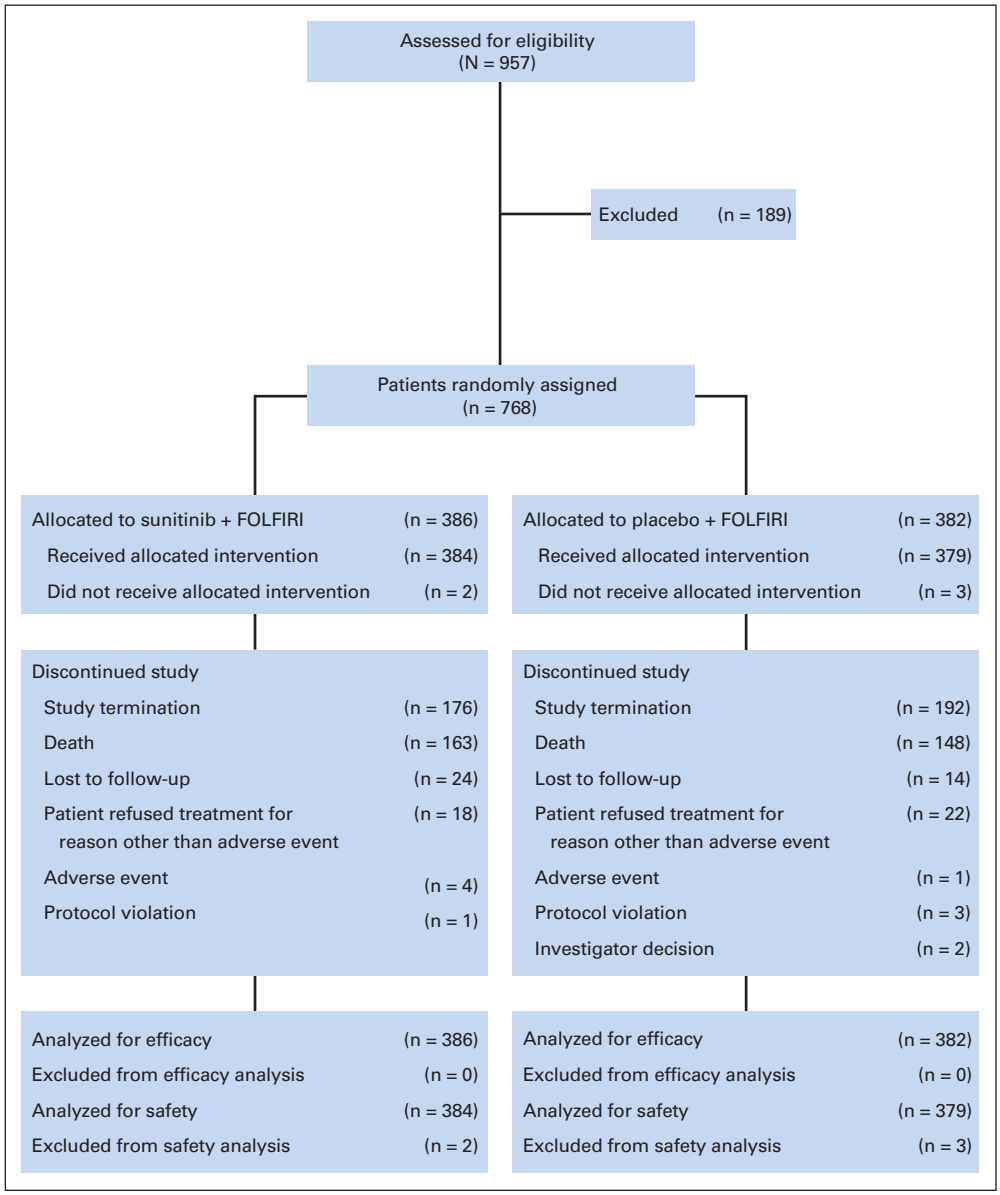

Fig 1. CONSORT diagram. FOLFIRI, fluorouracil, leucovorin, and irinotecan.

In total, 768 patients were randomly assigned to the sunitinib plus FOLFIRI arm (n = 386) or the placebo plus FOLFIRI arm (n = 382) at 128 centers worldwide (Europe, 58%; Asia-Pacific, 31%; Africa, 5%; South America 5%; Canada 1%). The efficacy analysis population comprised all 768 patients (Fig 1). Five patients did not receive study medication; the remaining 763 patients received at least one dose of study medication and comprised the safety analysis population (sunitinib plus FOLFIRI, n = 384; placebo plus FOLFIRI, n = 379). The data cutoff was April 16, 2010.

The treatment arms were well balanced for demographic, disease, and prior adjuvant treatment characteristics (Table 1). Overall, 38% (n = 146) and 23% (n = 89) of patients had sunitinib and placebo dose delays, respectively; 22% (n = 83) and 7% (n = 28) had a dose reduction, respectively. The resulting median relative dose-intensity was 86% (range, 7% to 120%) for sunitinib and 93% (range, 7% to 115%) for placebo. The median relative dose-intensity for irinotecan and fluorouracil was 75% to 76% (range, 21 to 112) and 91% to 92% (range, 25 to 113) in the sunitinib and placebo arms, respectively. Most patients discontinued treatment as a result of study termination (46% in the sunitinib plus FOLFIRI arm; 50% in the placebo plus FOLFIRI arm) or death (42% and 39%, respectively; Fig 1).

Efficacy

Median PFS was 7.8 months (95% CI, 7.1 to 8.4 months) in the sunitinib plus FOLFIRI arm and 8.4 months (95% CI, 7.6 to 9.2 months) in the placebo plus FOLFIRI arm (HR, 1.095; 95% CI, 0.892 to 1.344; one-sided stratified log-rank $P = .807$; (Fig 2A). At data cutoff, death or disease progression had occurred in 52% and 51% of patients in the sunitinib and placebo arms, respectively. In a post hoc Cox proportional hazards model, the following were not predictors of PFS: baseline characteristics (including serum lactate dehydrogenase levels, sex, and race), the presence of grade $\geq$ 3 sunitinib-related neutropenia or diarrhea, and exposure/duration of chemotherapy or blinded treatment (Table 2).

Table 1. Baseline Patient Characteristics

Characteristic	Sunitinib Plus FOLFIRI* (n = 386) No.	%	Placebo Plus FOLFIRI (n = 382) No.	%
Sex				
Male	222	58	203	53
Female	164	42	179	47
Age, years				
Median	59		58	
Range	25-83		25-82	
ECOG performance status				
0	212	55	204	53
1	174	45	178	47
No. of metastatic organ sites				
None	0		1†	< 1
1	127	33	147	38
> 1	259	67	234	61
Primary tumor site				
Colon	237	61	232	61
Rectum	149	39	150	39
No prior adjuvant treatment	307	80	296	77

Abbreviations: ECOG, Eastern Oncology Cooperative Group; FOLFIRI, fluorouracil, leucovorin, and irinotecan.
*Schedule 4/2, 4 weeks on treatment, followed by 2 weeks off; dosage, 37.5 mg per day.
†Protocol violation.

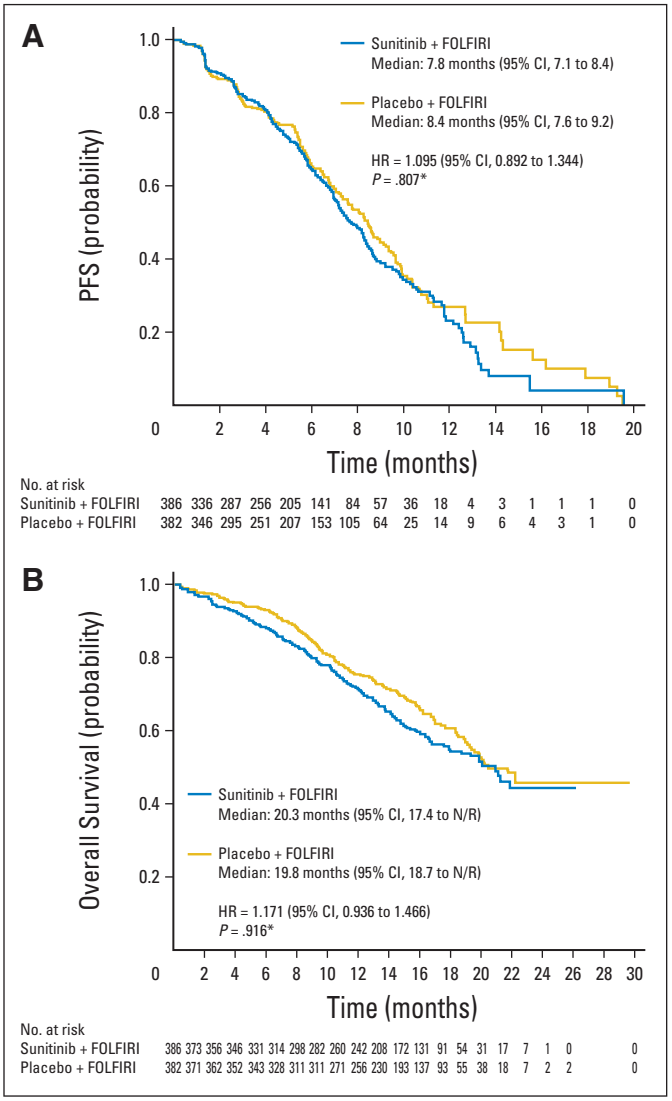

Fig 2. Kaplan-Meier estimates of (A) progression-free survival (PFS; independent central review) and (B) overall survival. A hazard ratio (HR) > 1 was in favor of the placebo plus FOLFIRI (fluorouracil, leucovorin, and irinotecan) arm. (*) *P* value from one-sided stratified log-rank test for superiority. N/R, not reached as a result of early study closure.

Median OS was 20.3 months (95% CI, 17.4 months to not reached [as a result of early study closure]) in the sunitinib plus FOLFIRI arm and 19.8 months (95% CI, 18.7 months to not reached) in the placebo plus FOLFIRI arm (HR, 1.171; 95% CI, 0.936 to 1.466; one-sided stratified log-rank $P = .916$; Fig 2B). At data cutoff, 42% of sunitinib-treated patients and 39% of placebo-treated patients had died. The ORR was 32% (124 of 386) for sunitinib plus FOLFIRI and 34% (128 of 382) for placebo plus FOLFIRI (Table 3).

Safety

The most commonly reported all-grade, nonhematologic AEs were diarrhea (66% and 50%; $P < .001$), nausea (50% and 48%; $P = .585$), and vomiting (39% and 35%; $P = .290$) for the sunitinib and placebo arms, respectively. AEs reported ≥ 10% more frequently with sunitinib than with placebo were diarrhea, stomatitis, hand-foot syndrome, and hypertension.

The most frequently reported nonhematologic grade ≥ 3 all-causality AEs were diarrhea (16%; $P = .002$ *v* placebo), fatigue (8%; $P < .001$ *v* placebo), and hand-foot syndrome (7%; $P < .001$ *v* placebo) for sunitinib plus FOLFIRI, and diarrhea (8%), vomiting (5%), and fatigue (3%) for placebo plus FOLFIRI (Table 4). In addition, sunitinib was associated with more grade ≥ 3 pooled stomatitis and related oral syndromes (9% *v* 2%; $P < .001$; Table 4). Grade ≥ 3 hypertension was observed in 3% of patients in the sunitinib arm compared with less than 1% in the placebo arm ($P = .053$). The most common grade ≥ 3 hematologic laboratory abnormalities were neutropenia (68% and 30%; $P < .001$) and thrombocytopenia (11% and 1%; $P < .001$) for the sunitinib and placebo arms, respectively (Table 4). Febrile neutropenia was reported in 7% and 3% ($P = .011$) of patients, respectively.

Sixteen patients died on study as a result of treatment-related grade 5 AEs. Twelve of these patients were in the sunitinib arm: sepsis/septic shock (four patients); febrile neutropenia/neutropenia (two); colonic obstruction (one); death from an unknown cause (one); peritonitis (one); respiratory failure (one); myocardial infarction with pulmonary embolism (one); or combined leukopenia, mucosal inflammation, and febrile neutropenia (one). Four patients had treatment-related grade 5 toxicities in the placebo arm: death from an unknown cause (one), hepatic failure (one), neutropenic sepsis (one), or pneumonia (one).

For sunitinib and placebo treatment, respectively, 24% (n = 91) and 11% (n = 43) of patients permanently discontinued treatment ($P < .001$), 61% (n = 233) and 35% (n = 131) experienced dose delays ($P < .001$), and 19% (n = 74) and 5% (n = 18) had dose reductions ($P < .001$). FOLFIRI dose reductions due to AEs occurred in 42% (n = 163) and 20% (n = 77) of patients in the sunitinib and

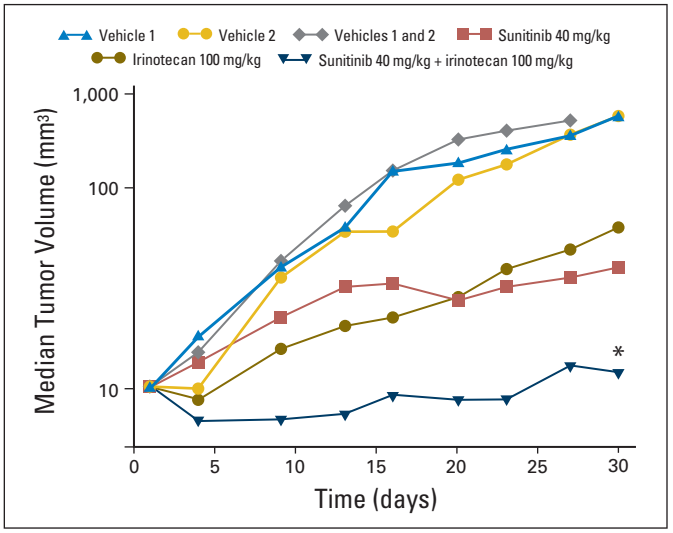

Fig 3. Growth inhibition of established LS174t human colon carcinoma xenografts in nude mice following treatment with sunitinib and irinotecan. LS174t human colon tumors were established in nude mice. When tumors reached an average size of 105 to 107 mm^3, animals were treated with either oral sunitinib 40 mg/kg daily until the end of the experiment, irinotecan 100 mg/kg administered intraperitoneally every 7 days for 3 weeks, both drugs in combination, or vehicle control (vehicle 1: carboxymethylcellulose used to deliver sunitinib; vehicle 2: 5% dextrose in water used to deliver irinotecan). Tumor volume was measured by using Vernier calipers on the indicated days, with the median tumor volume shown for groups of eight animals. (*) $P < .05$ versus sunitinib 40 mg/kg and irinotecan 100 mg/kg groups (one-way analysis of variance).

Table 2. Influence of Characteristics at Baseline and During Treatment on PFS (Cox model)

Characteristic	Sunitinib Plus FOLFIRI*	Placebo Plus FOLFIRI	HR	95% CI	P
Lactate dehydrogenase					
≤ Upper limit of normal	181	168	1.072	0.779 to 1.476	.667
> Upper limit of normal	183	175	1.028	0.767 to 1.379	.577
Sex					
Male	222	203	0.959	0.720 to 1.279	.391
Female	164	179	1.244	0.926 to 1.672	.928
Race					
White	260	246	1.085	0.843 to 1.397	.739
Asian	106	113	0.958	0.643 to 1.429	.419
Neutropenia grade					
< 3	129	—	0.880†	0.664 to 1.201	.209†
≥ 3	257	—			
Diarrhea grade					
< 3	329	—	1.362†	0.938 to 1.977	.948†
≥ 3	57	—			
Overall RDI of blinded treatment					
< Median	232	149	1.012	0.741 to 1.383	.533
≥ Median	152	229	1.144	0.859 to 1.525	.823
Overall RDI of irinotecan‡					
< Median	268	113	1.157	0.811 to 1.650	.789
≥ Median	116	266	1.374	1.006 to 1.875	.978

Abbreviations: FOLFIRI, fluorouracil, leucovorin, and irinotecan; HR, hazard ratio; PFS, progression-free survival; RDI, relative dose-intensity.
*Schedule 4/2, 4 weeks on treatment, followed by 2 weeks off; dosage, 37.5 mg per day.
†For grade ≥ 3 versus grade < 3 neutropenia or diarrhea in the sunitinib plus FOLFIRI arm.
‡Irinotecan reported as a representative component of FOLFIRI.

placebo arms, respectively ($P < .001$). The most common AEs resulting in sunitinib versus placebo dose delays/modifications were neutropenia (36% *v* 12%; $P < .001$), diarrhea (11% *v* 5%; $P = .003$), and leukopenia (9% *v* 3%; $P < .001$).

DISCUSSION

After many phase III trials, no benefit has been shown for combining conventional chemotherapy with VEGFR inhibitors in first-line mCRC treatment (despite preclinical data indicating that the combination of sunitinib and irinotecan was superior to either agent alone [$P < .05$; Fig 3; Pfizer, data on file]).[16,17] In this study, sunitinib plus FOLFIRI failed to demonstrate superior efficacy compared with placebo plus FOLFIRI in patients with mCRC. The PFS curves overlapped (Fig 2A), and median PFS was 7.8 months (95% CI, 7.1 to 8.4 months) in the sunitinib plus FOLFIRI arm and 8.4 months (95% CI, 7.6 to 9.2 months) in the placebo plus FOLFIRI arm. Although the placebo plus FOLFIRI results are comparable with historical data,[4] the median PFS of 7.8 months (95% CI, 7.1 to 8.4 months) in the sunitinib plus FOLFIRI arm is in contrast to results from studies of other targeted agents in combination with FOLFIRI in treatment-naïve patients with mCRC. Bevacizumab plus FOLFIRI, for example, yielded a median PFS of 11.1 months in a phase IV study,[18] 11.2 months in a randomized phase III study,[19] and 12.8 months in a single-arm phase II study.[20]

Similarly, median OS in this study was approximately 20 months in both arms, showing no statistical evidence of superiority for sunitinib. However, at the time of the analysis, the survival data were not mature. After the data monitoring committee made its recommendation, the majority of patients remaining in survival follow-up were removed from the study (approximately 40% of patients had died in both arms), and as a result, these findings should be interpreted

Table 3. Best Objective Response Based on RECIST (independent central review)

Variable	Sunitinib Plus FOLFIRI* (n = 386) No.	%	Placebo Plus FOLFIRI (n = 382) No.	%
Best objective response				
Complete response	0		1	< 1
Partial response	124	32	127	33
Stable disease	200	52	201	53
Progressive disease	25	6	32	8
Not evaluable	25	6	16	4
Missing	12	3	5	1
Objective response rate	124	32†	128	34

Abbreviations: FOLFIRI, fluorouracil, leucovorin, and irinotecan; RECIST, Response Evaluation Criteria in Solid Tumors.
*Schedule 4/2, 4 weeks on treatment, followed by 2 weeks off; dosage, 37.5 mg per day.
†$P = .683$ versus placebo plus FOLFIRI.

Table 4. Grade ≥ 3 Adverse Events and Hematologic Abnormalities Reported in ≥ 5% of Patients or of Clinical Interest, Regardless of Causality

Adverse Events and Hematologic Abnormalities	Sunitinib Plus FOLFIRI* (n = 384)		Placebo Plus FOLFIRI (n = 379)		
	No. of Patients	%	No. of Patients	%	P
Nonhematologic adverse events					
Diarrhea	60	16	31	8	.002
Fatigue	31	8	10	3	< .001
Hand-foot syndrome	25	7	2	< 1	< .001
Vomiting	23	6	18	5	.448
Hematologic abnormalities					
Neutropenia†	214 of 316	68	89 of 296	30	< .001
Thrombocytopenia†	44 of 383	11	4 of 378	1	< .001
Anemia	33 of 384	9	19 of 379	5	.050
Febrile neutropenia	28 of 384	7	12 of 379	3	.011
Adverse events of special interest					
Stomatitis, oral discomfort, and related oral syndromes‡	35	9	7	2	< .001
Hypertension	10	3	3	< 1	.053
Skin discoloration	1	< 1	0		.320
Thrombotic events§	16	4	22	6	.298

Abbreviation: FOLFIRI, fluorouracil, leucovorin, and irinotecan.
*Schedule 4/2, 4 weeks on treatment, followed by 2 weeks off; dosage, 37.5 mg per day.
†Based on laboratory data.
‡Includes aphthous stomatitis, gingival pain, gingivitis, glossitis, glossodynia, mouth ulceration, mucosal dryness, mucosal inflammation, oral pain, stomatitis, and swollen tongue.
§Includes deep vein thrombosis, subclavian vein thrombosis, thrombosis, venous thrombosis, pulmonary embolism, and myocardial ischemia.

with caution. In addition, the ORR in the sunitinib plus FOLFIRI arm failed to be significantly better than the ORR in the placebo plus FOLFIRI arm (32% *v* 34%; $P = .683$).

In line with previous observations,[11,12] AEs reported in the sunitinib arm of this study included gastrointestinal symptoms (diarrhea, nausea, and vomiting), fatigue, skin toxicities (hand-foot syndrome), hematologic toxicities, and hypertension. Sunitinib in combination with chemotherapy was also associated with higher frequencies of grade ≥ 3 AEs and laboratory abnormalities compared with placebo (including diarrhea, stomatitis and related oral syndromes, fatigue, hand-foot syndrome, neutropenia, febrile neutropenia, anemia, and thrombocytopenia) and more treatment-related deaths (12 *v* four). Grade ≥ 3 hypertension was observed in 3% of sunitinib-treated patients. In addition, more patients had dose delays, dose reductions, or permanent discontinuations of sunitinib treatment due to AEs compared with placebo (all $P < .001$). An increase in rates of grade ≥ 3 AEs negatively influenced treatment administration in the experimental arm.

A post hoc analysis was performed with regard to potential clinical or biologic factors predictive of clinical benefit with sunitinib treatment. Subgroup analyses evaluated baseline characteristics (including race, sex, and lactate dehydrogenase levels), as well as the presence of grade ≥ 3 sunitinib-related AEs (neutropenia or diarrhea) and exposure to or duration of chemotherapy or blinded treatment. Toxicity was explored only within the sunitinib arm to identify differences between patients who responded with an HR below 1 and those with an HR above 1. No clear predictors of PFS were identified. In contrast to the CONFIRM 2 trial [Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases], in which the VEGFR inhibitor vatalanib (PTK787) was combined with chemotherapy,[21] lactate dehydrogenase levels were not predictive of PFS in this study.

Other factors potentially contributing to the observed outcome include the relatively low median dose-intensity of both FOLFIRI (75% to 76%) and sunitinib (86%) in the sunitinib arm, compared with FOLFIRI (91% to 92%) and placebo (93%) in the placebo arm. The lower dose-intensity of FOLFIRI might have resulted from increased toxicity (eg, diarrhea and neutropenia) with the addition of sunitinib, which could have reduced the chemotherapy effect in the experimental arm. Similarly, low sunitinib dose-intensity in this study may have limited the ability to demonstrate a benefit, a possibility supported by a meta-analysis indicating that increased exposure to sunitinib is associated with improved clinical outcome.[22] An increased exposure might be achieved when sunitinib monotherapy is scheduled rather than combination treatment. In addition, mCRC cells may not be particularly dependent on the signaling pathways inhibited by sunitinib. If the inhibited kinases are not relevant to the cancer being treated, it may be detrimental to block multiple targets. Conversely, additional proangiogenic factors, independent of VEGF, may be implicated in tumor progression.[20]

In summary, sunitinib 37.5 mg per day on schedule 4/2 combined with FOLFIRI is not recommended for patients with treatment-naïve mCRC, because the addition of sunitinib increased toxicity and did not improve PFS, OS, or ORR compared with placebo.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ORIGINAL REPORT

Histomolecular Phenotypes and Outcome in Adenocarcinoma of the Ampulla of Vater

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ABSTRACT

Purpose
Individuals with adenocarcinoma of the ampulla of Vater demonstrate a broad range of outcomes, presumably because these cancers may arise from any one of the three epithelia that converge at that location. This variability poses challenges for clinical decision making and the development of novel therapeutic strategies.

Patients and Methods
We assessed the potential clinical utility of histomolecular phenotypes defined using a combination of histopathology and protein expression (CDX2 and MUC1) in 208 patients from three independent cohorts who underwent surgical resection for adenocarcinoma of the ampulla of Vater.

Results
Histologic subtype and CDX2 and MUC1 expression were significant prognostic variables. Patients with a histomolecular pancreaticobiliary phenotype (CDX2 negative, MUC1 positive) segregated into a poor prognostic group in the training (hazard ratio [HR], 3.34; 95% CI, 1.69 to 6.62; $P < .001$) and both validation cohorts (HR, 5.65; 95% CI, 2.77 to 11.5; $P < .001$ and HR, 2.78; 95% CI, 1.25 to 7.17; $P = .0119$) compared with histomolecular nonpancreaticobiliary carcinomas. Further stratification by lymph node (LN) status defined three clinically relevant subgroups: one, patients with histomolecular nonpancreaticobiliary (intestinal) carcinoma without LN metastases who had an excellent prognosis; two, those with histomolecular pancreaticobiliary carcinoma with LN metastases who had a poor outcome; and three, the remainder of patients (nonpancreaticobiliary, LN positive or pancreaticobiliary, LN negative) who had an intermediate outcome.

Conclusion
Histopathologic and molecular criteria combine to define clinically relevant histomolecular phenotypes of adenocarcinoma of the ampulla of Vater and potentially represent distinct diseases with significant implications for current therapeutic strategies, the ability to interpret past clinical trials, and future trial design.

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INTRODUCTION

Adenocarcinoma of the ampulla of Vater is the second most common malignancy of the periampullary region and accounts for up to 30% of all pancreaticoduodenectomies.[1,2] The broad range of outcomes for patients with adenocarcinoma of the ampulla of Vater[3-8] impairs the interpretation of clinical trials and hampers clinical decision making. This is perhaps not surprising, because they may arise from any one of the three epithelia (duodenal, biliary, or pancreatic) that converge at this location.

The inability to predict individual outcomes for cancers in this anatomic location has made aspects of clinical decision making difficult with regard to the aggressiveness of therapy and the choice of appropriate chemotherapeutic strategies. Randomized, controlled trials[9-11] and single-institution cohorts[12-18] grouping all adenocarcinomas together have failed to definitively demonstrate a survival benefit for adjuvant chemotherapy. Some studies have suggested that adenocarcinoma of the ampulla of Vater may be subdivided based on histologic appearances[19,20] and GI markers such as caudal-type

homeodomain transcription factors, apomucins, and cytokeratins[21-23]; however, the potential clinical utility of such a classification has not been investigated.

This is problematic in interpreting clinical trial data because different phenotypes are likely to have a differential response to specific chemotherapeutics. Although both gemcitabine and fluorouracil (FU) may be effective in pancreatic cancer, gemcitabine is not known for its efficacy in carcinomas of intestinal origin.[24] For example, the ESPAC-3 (V2) adjuvant therapy trial compared adjuvant FU with gemcitabine or observation for resected ampullary cancer; despite an overall survival benefit with adjuvant chemotherapy on multivariate analysis, there was no difference in response between pancreaticobiliary and intestinal subtypes based on histology alone in a posthoc analysis.[25]

Here, we validate previously described prognostic factors[21] and define distinct phenotypes of adenocarcinoma of the ampulla of Vater based on a combination of molecular and histopathologic features using three independent cohorts of patients. Such histomolecular stratification may better delineate prognostic groups, aid in the refinement of current therapeutic strategies, better interpret past clinical trials, and facilitate future trial design.

PATIENTS AND METHODS

Patients and Data Acquisition

Training cohort. Clinicopathologic and outcome data for a cohort of 72 consecutive patients with a diagnosis of adenocarcinoma of the ampulla of Vater who underwent Whipple's pancreaticoduodenectomy with curative intent between 1993 and 2008 were accrued from six teaching hospitals associated with the Australian Pancreatic Cancer Genome Initiative (APGI; www.pancreaticcancer.net.au), Sydney, New South Wales, Australia (online-only Appendix; Table 1; Data Supplement). This was designated the Sydney training cohort.

Validation cohorts. Two additional cohorts of 90 and 46 patients, respectively, were prospectively acquired at the West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, United Kingdom (between 1992 and 2010), and the University Hospital of Verona, Verona, Italy (between 1992 and 2010). These were designated as the Glasgow validation cohort and the Verona validation cohort, respectively. Ethical approval for the acquisition of data and biologic material was obtained from the human research ethics committee at each participating institution (Appendix, online only). Informed consent was obtained from each participant for the validation cohorts but was not required by the human research ethics committee for the retrospective patient cases in the Sydney cohort.

Adenocarcinoma of the ampulla of Vater was verified and all pathologic features reviewed independently by two specialist pancreatic histopathologists who were blinded to clinical outcomes. This was performed by A.J.G. and A.C. for the Sydney training cohort, A.K.F. and K.A.O. for the Glasgow validation cohort, and A.J.G. and A.S. for the Verona validation cohort. Tumors were classified as either of intestinal, pancreaticobiliary, or mixed histologic subtype. The intestinal histologic subtype was defined by tall columnar cells forming elongated glands (similar to colorectal adenocarcinoma), whereas pancreaticobiliary morphology was defined by cells with rounded nuclei forming rounded glands, similar to the majority of pancreaticobiliary carcinomas (Figs 1A to 1F). Mixed tumors contained $>$ 10% of both histologic types and overall accounted for only 7% of samples. Tumors were staged according to the American Joint Committee on Cancer (AJCC) Staging Manual, seventh edition.[26]

Tissue Microarrays and Immunohistochemistry

Tissue microarrays were constructed from formalin-fixed, paraffin-embedded material, with each specimen represented by a minimum of 3- $\times$ 1-mm tissue cores. Immunohistochemistry was performed

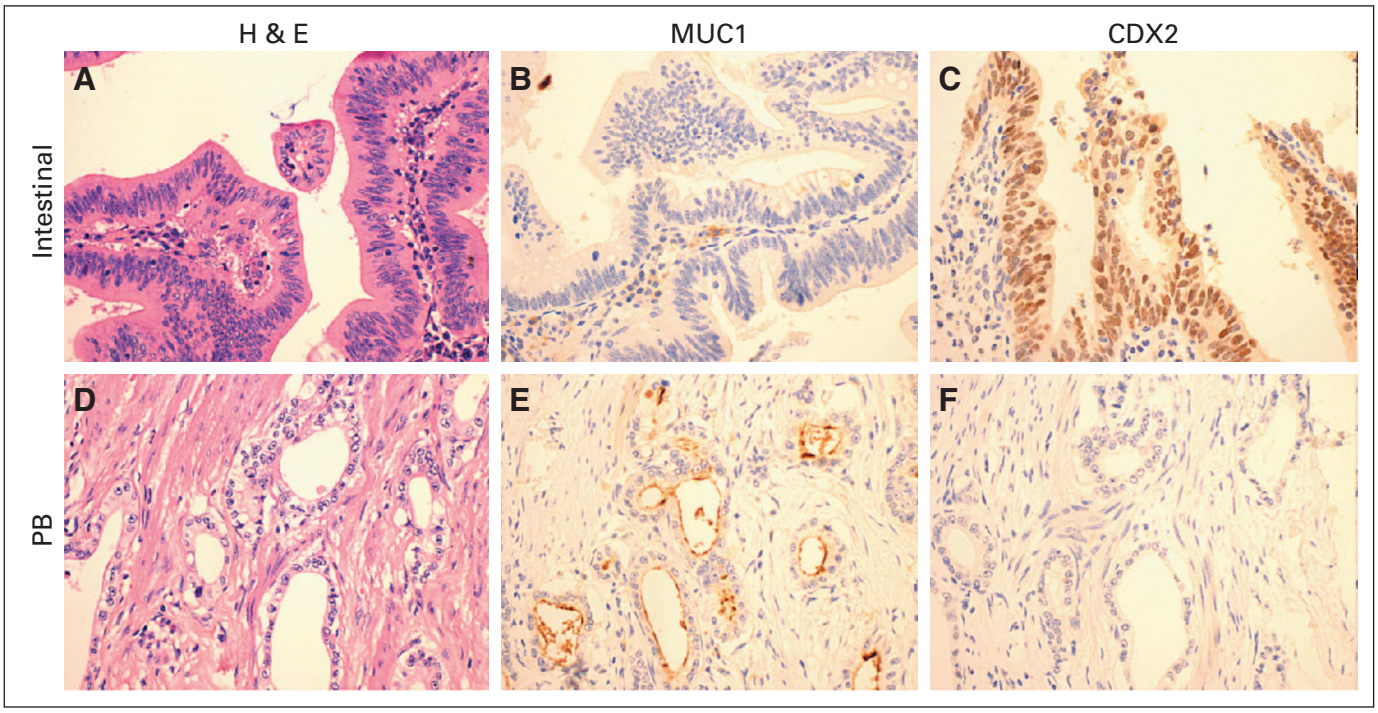

Fig 1. Serial sections stained with hematoxylin and eosin (H & E). (A, B, C) MUC1 and CDX2 in one patient case displaying the typical histomolecular intestinal phenotype, and (D, E, F) one patient case displaying the typical histomolecular pancreaticobiliary (PB) phenotype. (A) The intestinal-type morphology is characterized by tall columnar cells forming elongated glands, (B) negative for MUC1 with (C) positive nuclear CDX2 immunostaining, whereas (D) pancreaticobiliary morphology is characterized by cells with rounded nuclei forming rounded glands, (E) with positive apical MUC1 immunostaining and (F) negative CDX2. All original magnifications at $\times$400.

on 4-μm serial sections mounted on SuperFrost slides (Menzel-Gläser, Braunschweig, Germany).

CDX2, MUC1, MUC2, CK7, and CK20 Immunohistochemistry

Five routinely used immunohistochemical markers were examined based on their routine use to define the origin of adenocarcinomas where the primary site of carcinoma is unknown (cytokeratins CK7 and CK20 and epithelial mucins MUC1 and MUC2[27,28]) or to distinguish adenocarcinomas of intestinal type from tumors that arise elsewhere (CDX2).[29] The Appendix (online only) provides information for each antibody, dilution, and retrieval method. All five biomarkers were tested in the Sydney training cohort, but only the two that were prognostic (CDX2 and MUC1) were tested in the validation cohorts.

Immunohistochemistry Scoring

Immunostaining (Figs 1A to 1F) was scored semiquantitatively as follows: 0 (absent staining), 1+ (focal weak staining), and 2+ (strong diffuse staining). For CDX2, in addition to intensity (0 to 3), the percentage of positive staining cells was also determined. Standardization of scoring was achieved by comparison of scores between at least two specialist pancreatic histopathologists and/or translational researchers experienced in peripancreatic pathology (A.J.G., A.S., and A.C. for Sydney and Verona cohorts; A.K.F., K.A.O., N.B.J., and M.A.A.M. for the Glasgow cohort). Any discrepancies were resolved by consensus after conferencing. Positive CDX2 expression was defined as a modified H score (intensity $\times$ percentage of positive cells) of $>$ 35. Positive MUC1, MUC2, and CK20 expression was defined as any positive staining; positive CK7 expression was defined as staining intensity of 2.

Statistical Analysis

Median survival was estimated using the Kaplan-Meier method, and the difference was tested using the log-rank test. The 5-year survival rate was estimated using the life-table method. P values $< .05$ were considered statistically significant. Clinicopathologic variables analyzed with a P value $< .25$ on log-rank test were entered into Cox proportional hazards multivariate analysis. Statistical analysis was performed using StatView 5.0 software (Abacus Systems, Berkeley, CA). Overall (Sydney and Verona cohorts) and disease-specific survival (Glasgow cohort) were used as the primary end points.

RESULTS

Cohort Characteristics

Characteristics of all cohorts are summarized in Table 1, with detailed descriptions provided in the Data Supplement.

Clinicopathologic and Molecular Prognostic Factors

Sydney training cohort. Factors associated with better survival on univariate analysis included T1/T2 tumors compared with T3/T4 tumors (median survival, 152.4 *v* 57.0 months; $P = .0334$), absence of lymph node metastases (152.4 *v* 32.1 months; $P = .0011$), and tumors of histopathologic intestinal or mixed subtype compared with pancreaticobiliary subtype (115.5 *v* 22.0 months; $P = .0169$; mixed tumors were grouped with the intestinal subtype). The overall AJCC pathologic stage was also associated with outcome, with median survival for stages I, II, and III of 152.4, 69.5, and 20.5 months, respectively ($P = .003$). Adjuvant chemotherapy was administered to 17 patients and was not associated with improved survival (median survival, 57.0 *v* 72.0 months; $P = .7384$). Of the five molecular markers examined (CDX2, MUC1, MUC2, CK7, and CK20), positive CDX2 expression (172.8 *v* 69.5 months; $P = .0368$) and negative MUC1 expression (115.5 *v* 45.0 months; $P = .0315$) were associated with longer survival (Table 1; Data Supplement).

Glasgow validation cohort. Factors associated with better survival on univariate analysis included T1/T2 tumors compared with T3/T4 tumors (median survival, 90.4 *v* 26.2 months; $P = .0097$), absence of lymph node metastases (120.9 *v* 17.6 months; $P < .001$), well/moderate tumor differentiation (47.5 *v* 18.1 months; $P = .0095$), tumor size $\leq$ 20 mm (47.7 *v* 26.0 months; $P = .0462$), tumors of histopathologic intestinal or mixed subtype compared with pancreaticobiliary subtype (69.0 *v* 23.9 months; $P < .001$), and absence of vascular space invasion (47.7 *v* 13.6 months; $P < .001$). The overall AJCC pathologic stage was also associated with outcome, with median survival for stages I, II, and III of not applicable (NA), 27.0, and 11.1 months, respectively ($P < .001$; NA indicates median survival was not reached). Adjuvant chemotherapy was administered to 21 patients and was not associated with improved survival (median survival, 33.0 *v* 29.0 months; $P = .6800$). Positive CDX2 expression (NA *v* 24.2 months; $P < .001$) and negative MUC1 expression (67.0 *v* 20.1 months; $P = .0055$) were associated with longer survival (Table 1; Data Supplement).

Verona validation cohort. Factors associated with better survival on univariate analysis included absence of lymph node metastases (NA *v* 36.0 months; $P = .0056$) and tumors of histopathologic intestinal or mixed subtype compared with pancreaticobiliary subtype (94.0 *v* 33.3 months; $P = .0246$). The overall AJCC pathologic stage was also associated with outcome, with median survival for stages I, II, and III of NA, 102.3, and 32.0 months, respectively ($P = .0019$). Positive CDX2 expression (94.0 *v* 33.3 months; $P = .0966$) and negative MUC1 expression (NA *v* 36.0 months; $P < .001$) trended with or was associated with better survival (Table 1; Data Supplement).

Histopathologic and Molecular Criteria Combine to Define Distinct Phenotypes of Adenocarcinoma of the Ampulla of Vater

CDX2 is a transcription factor that regulates axial development and intestinal differentiation, is expressed almost exclusively in intestinal epithelium,[29,30] and is associated with better survival in ampullary cancers.[21] Conversely, MUC1 expression is highly prevalent in cancers of pancreaticobiliary origin.[28,31] On the basis of the hypothesis that these markers represent different molecular phenotypes, the histologic subtypes were combined with differential marker expression.

Patients were grouped into the histomolecular pancreaticobiliary or nonpancreaticobiliary (intestinal) phenotype. The pancreaticobiliary phenotype was defined as a tumor of histologic pancreaticobiliary subtype with negative CDX2 and positive MUC1 immunostaining. The nonpancreaticobiliary (intestinal) phenotype encompassed the remainder. In the Sydney training cohort, a histomolecular pancreaticobiliary phenotype was associated with a poor prognosis on both univariate (median survival, 16.1 *v* 115.5 months; $P < .001$; Table 1; Fig 2A) and multivariate analyses (HR, 3.40; 95% CI, 1.71 to 6.76; $P < .001$; Table 2; Data Supplement). The only other independent prognostic factor was the presence of lymph node metastases (HR, 3.19; 95% CI, 1.54 to 6.58; $P = .0017$). These two independent prognostic variables were used to stratify the cohort into three prognostic groups (Fig 2D). First, the group of patients with a histomolecular nonpancreaticobiliary (intestinal) phenotype and no lymph node involvement had an excellent prognosis, with a 5-year survival of 88.4% and median survival of 172.8 months. Second, the group of patients with a histomolecular pancreaticobiliary phenotype and lymph node metastases had a poor prognosis, with a 5-year survival of 20.0% and median survival of 7.4 months. Third, the remaining patients (histomolecular nonpancreaticobiliary [intestinal] phenotype with lymph

Table 1. Clinicopathologic Parameters and Outcome for All Cohorts

Variable	Sydney Cohort (n = 72)				Glasgow Cohort (n = 90)				Verona Cohort (n = 46)			
	No.	%	Median OS (months)	Log-Rank *P*	No.	%	Median DSS (months)	Log-Rank *P*	No.	%	Median OS (months)	Log-Rank *P*
Sex				.6779				.5411				.0475
Male	42	58.3	72.7		53	58.9	33.0		25	54.3	36.0	
Female	30	41.7	152.4		37	41.1	28.3		21	45.7	102.3	
Age, years												
Mean			66.1				63.5				62.9	
Median			68.0				65.1				64.0	
Range			34.0-88.0				37.7-77.5				38.0-79.0	
Follow-up												
Median			84.0				81.0				105.9	
Range			0.3-193				0.4-240.0				7.0-145.1	
Outcome												
Death AC	30	41.6			54	60.0			25	54.3		
Death other	4	5.6			7	7.8			2	4.3		
Death unknown	2	2.8			0	0.0			0	0.0		
Alive	36	50.0			29	32.2			19	41.3		
Overall stage				.0030				< .001				.0019
I	17	23.6	152.4		19	21.1	NA		7	15.2	NA	
II	39	54.2	69.5		55	61.1	27.0		17	37.0	102.3	
III	16	22.2	20.5		16	17.8	11.1		22	47.8	32.0	
T stage				.0334*				.0097*				.1248*
T1	10	13.9			6	6.7			2	4.3		
T2	20	27.8	152.4		31	34.4	90.4		7	15.2	NA	
T3	26	36.1			37	41.1			12	26.1		
T4	16	22.2	57.0		16	17.8	26.2		25	54.3	43.9	
N stage				.0011				< .001				.0056
N0	36	50.0	152.4		39	43.3	120.9		16	34.8	NA	
N1	36	50.0	32.1		51	56.7	17.6		30	65.2	36.0	
Grade				.1063†				.0095†				.3066†
I	6	8.3			4	4.4			2	4.3		
II	35	48.6	101.4		57	63.3	47.5		33	71.7	51.9	
III	28	38.9			29	32.2			10	21.7		
IV	3	4.2	25.1		0	0.0	18.1		1	2.2	33.3	
Tumor size, mm				.9858				.0462				.0152
≤ 20	37	51.4	72.0		45	50.0	47.7		7	15.2	19.0	
> 20	35	48.6	115.5		45	50.0	26.0		39	84.8	69.9	
Margins‡				.5205				.0776				.9490
Clear	68	94.4	101.4		61	67.8	35.0		40	87.0	51.8	
Involved	4	5.6	20.5		29	32.2	27.5		6	13.0	62.0	
Subtype				.0169§				< .001§				.0246§
Intestinal	41	56.9			44	48.9			20	43.5		
Mixed	5	6.9	115.5		5	5.6	69.0		4	8.7	94.0	
Pancreaticobiliary	26	36.1	22.0		41	45.6	23.9		22	47.8	33.3	
Perineural invasion				.3216				.0623				.0510
Negative	52	72.2	101.4		60	66.7	32.1		22	47.8	94.0	
Positive	20	27.8	57.0		30	33.3	23.9		24	52.2	42.3	
Vascular invasion				.0818				< .001				.0817
Negative	22	30.6	115.5		63	70.0	47.7		23	50.0	94.0	
Positive	50	69.4	69.5		27	30.0	13.6		23	50.0	36.0	
Chemotherapy				.7384				.6800				.6256
Adjuvant	17	27.4	57.0		21	23.3	33.0		26	56.5	43.9	
No adjuvant	45	72.6	72.0		69	76.7	29.0		20	43.4	69.9	
CDX2 expression‖				.0368				< .001				.0966
Negative	51	70.8	69.5		54	65.0	24.2		18	40.0	33.3	
Positive	21	29.2	172.8		29	35.0	NA		27	60.0	94.0	
MUC1 expression¶				.0315				.0055				< .001
Negative	29	40.3	115.5		51	57.3	67.0		15	32.6	NA	
Positive	43	59.7	45.0		38	42.7	20.1		31	67.4	36.0	

(continued on following page)

Table 1. Clinicopathologic Parameters and Outcome for All Cohorts (continued)

Variable	Sydney Cohort (n = 72)				Glasgow Cohort (n = 90)				Verona Cohort (n = 46)			
	No.	%	Median OS (months)	Log-Rank *P*	No.	%	Median DSS (months)	Log-Rank *P*	No.	%	Median OS (months)	Log-Rank *P*
Histomolecular phenotype				< .001				< .001				.0088
Intestinal, CDX2 positive, or MUC1 negative	54	75.0	115.5		66	80.5	67.0		33	73.3	94.0	
PB, CDX2 negative, and MUC1 positive	18	25.0	16.1		16	19.5	11.9		12	26.7	30.9	
Histomolecular phenotype and LN status				< .001				< .001				< .001
Non-PB (intestinal), LN negative	28	43.9	172.8		36	43.9	NA		16	35.6	NA	
Non-PB (intestinal), LN positive or PB, LN negative	34	40.2	57.0		33	40.2	26.2		17	37.8	51.8	
PB, LN positive	10	15.9	7.4		13	15.9	11.9		12	26.7	30.9	

Abbreviations: AC, ampullary cancer; DSS, disease-specific survival; LN, lymph node; NA, not applicable (median survival not reached); OS, overall survival; PB, pancreaticobiliary.

*T1/2 versus T3/4 for survival analyses based on American Joint Committee on Cancer TNM Staging System, Ampullary Cancer.

†Grade I/II versus III/IV for survival analyses.

‡Microscopically involved margin (R1) is defined as 0 mm in the Sydney and Verona cohorts and as 1 mm in the Glasgow cohort.

§Intestinal and mixed subtypes versus PB subtype for survival analyses.

‖Positive expression of CDX2 was defined as modified H score > 35.

¶Positive expression of MUC1 was defined as any staining.

node metastases or histomolecular pancreaticobiliary phenotype with no lymph node involvement) had an intermediate prognosis, with a 5-year survival of 46.9% and median survival of 57.0 months.

The poorest prognostic histomolecular phenotypic subgroup (pancreaticobiliary subtype, CDX2 negative and MUC1 positive) was defined using a combination of both histologic and molecular criteria. Using the same concept, although the numbers were small, the best prognostic phenotypic subgroup could also be identified. Patients who had a tumor of histomolecular intestinal phenotype (histological intestinal subtype and CDX2 positive) with no lymph node metastases had an extremely good prognosis, with a 5-year survival of 100% and median survival of 172.8 months (Data Supplement). To validate these findings, two comparable but independent cohorts of patients with resected adenocarcinoma of the ampulla of Vater were examined using identical histologic and molecular criteria.

Glasgow validation cohort. Histomolecular phenotypes defined in the Sydney training cohort cosegregated with outcomes (histomolecular nonpancreaticobiliary *v* pancreaticobiliary; median survival, 67.0 *v* 11.9 months; $P < .001$; Fig 2B). Further stratification with lymph node status again stratified the cohort into three distinct prognostic groups, recapitulating the findings of the Sydney training cohort (Fig 2E). First, the group of patients with histomolecular nonpancreaticobiliary (intestinal) phenotype and no lymph node involvement again had an excellent prognosis, with a 5-year survival of 66.7% and median survival that was not reached. Second, the group of patients with a histomolecular pancreaticobiliary phenotype and lymph node metastases had a poor prognosis, with a median survival of 11.9 months and no 5-year survivors. Third, the remaining patients had an intermediate prognosis, with a 5-year survival of 28.6% and median survival of 26.2 months. Once again, patients with a histomolecular intestinal phenotype without lymph node metastases had an extremely good prognosis, with a 5-year survival of 90% and median survival that was not reached (Data Supplement).

Verona validation cohort. These relationships with outcome were also apparent in the Verona validation cohort. The two prognostic groups of histomolecular nonpancreaticobiliary and pancreaticobiliary phenotypes had median survivals of 94.0 and 30.9 months, respectively ($P = .0088$; Fig 2C). Further stratification with lymph node status again divided the cohort into three distinct prognostic groups (Fig 2F). First, the group of patients with histomolecular nonpancreaticobiliary (intestinal) phenotype and no lymph node involvement again had an excellent prognosis, with a 5-year survival of 87.5% and median survival that was not reached. The other two groups had 5-year and median survivals of 41.7% and 51.8 months and 16.7% and 30.9 months, respectively. Patients with a histomolecular intestinal phenotype carcinoma without lymph node metastases again had a favorable prognosis (5-year survival, 92.3%; median survival, 102.3 months; Data Supplement). REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) criteria[32] summaries for CDX2 and MUC1 are presented in Table 3.

DISCUSSION

Defining clinically and biologically relevant phenotypes leads to improvements in overall outcomes through facilitating clinical decision making. Here, we identify distinct clinically relevant phenotypes by refining a histologic classification with molecular criteria to define histomolecular phenotypes. These results were independently validated in two additional cohorts of patients, where histomolecular phenotyping again delineated these distinct prognostic groups. A robust histomolecular classification that is prognostic across several independent cohorts in a heterogeneous cancer type compared with conventional histopathologic classification indirectly supports its use over more variable clinicopathologic factors. Such variability in clinicopathologic factors was seen in these cohorts and has occurred even in large, phase III, randomized, controlled clinical trials, such as RTOG (Radiation Therapy Oncology Group) -9704, ESPAC (European Study Group for Pancreatic Cancer) -1, ESPAC-3, and CONKO (Charité Onkologie) -001. This classification is potentially important in a disease with a broad range of outcomes such as adenocarcinoma of the ampulla of Vater. First, patients could be better selected for

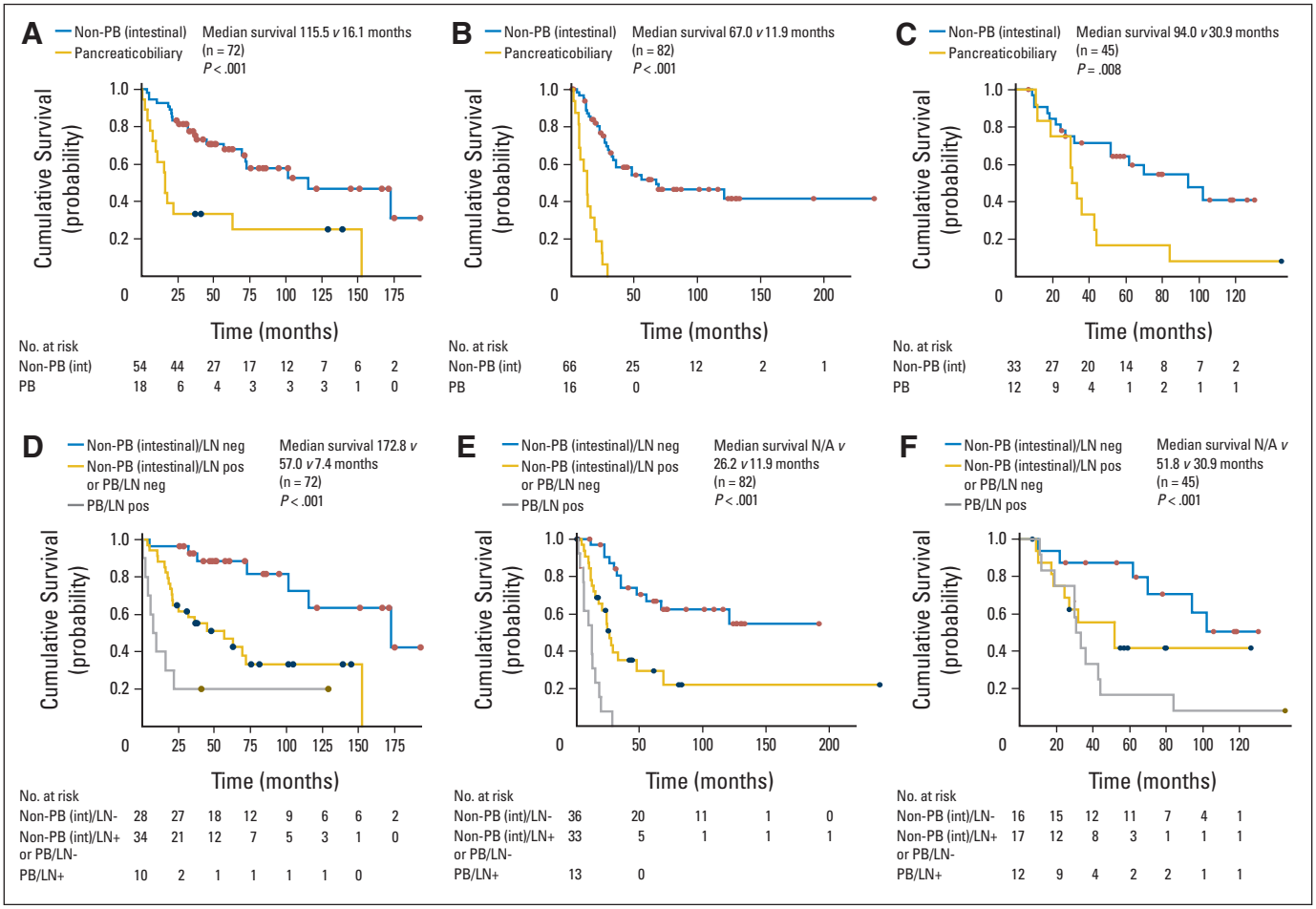

Fig 2. Kaplan-Meier survival curves for the (A, D) Sydney training cohort and (B, E) Glasgow and (C, F) Verona validation cohorts showing (A, B, C) histomolecular phenotypes and (D, E, F) subsequent stratification of each cohort into three prognostic phenotypes using histomolecular phenotyping and lymph node (LN) status. INT, intestinal; N/A, not applicable; OR, median survival not reached; PB, pancreaticobiliary.

surgery, so aggressive and radical surgery could be justified in patients with a tumor of histomolecular intestinal (nonpancreaticobiliary) phenotype on biopsy and a good prognosis expected if resected with clear margins. Second, patients could be better selected for adjuvant chemotherapy, because it is likely that they respond differently to different chemotherapeutic regimens and should be treated differently. Adjuvant gemcitabine chemotherapy would likely only benefit the pancreaticobiliary phenotype, not the intestinal phenotype. This heterogeneity in response may also make it difficult to detect a statistically significant difference in clinical trials of unselected patients. The outcome of a trial would depend on the proportion of each phenotype within the recruited cohort, and the histomolecular distinction could be used to target specific patient subgroups. In addition, it is difficult to detect efficacy of an adjuvant strategy in patients who have an excellent prognosis with surgery alone, and the inclusion of such patients would inadvertently underpower clinical trials.

Table 2. Multivariate Analyses: Final Models for All Cohorts

Variable	HR	95% CI	*P*
Sydney cohort (n = 72)			
Positive LN metastases	3.19	1.54 to 6.58	.0017
PB histomolecular phenotype	3.40	1.71 to 6.76	< .001
Glasgow cohort (n = 82)			
Tumor stage (T3/T4)	2.27	1.09 to 4.74	.0280
Positive LN metastases	2.63	1.36 to 5.10	.0042
PB histomolecular phenotype	5.65	2.77 to 11.5	< .001
Verona cohort (n = 45)			
Positive LN metastases	3.51	1.37 to 8.93	.0086

Abbreviations: HR, hazard ratio; LN, lymph node; PB, pancreaticobiliary.

This could have contributed to the negative result of the ESPAC-3 (V2) adjuvant therapy trial for periampullary cancer,[25] where posthoc analysis based on histologic subtype alone did not identify differential treatment responsiveness. In addition, the potential benefit of adjuvant chemotherapy was only demonstrated in multivariate analysis when adjusted for other prognostic variables, suggesting that poor-prognosis tumors were potentially associated with responsiveness. This is also supported by evidence from single-institutional studies, showing a survival benefit with adjuvant chemotherapy in patients with unfavorable prognostic features.[12,13,15-18] Additional analyses using a histomolecular classifier should be encouraged and may be informative because this would potentially better differentiate underlying tumor biology. In our cohorts, fewer than

Table 3. REMARK Summary for CDX2 and MUC1

Category	Summary
Introduction	
Markers examined	CDX2 (caudal type homeobox 2)
	MUC1 (Mucin 1, cell surface associated)
Objective	Assess potential of CDX2 and MUC1 expression as markers of prognosis in patients with adenocarcinoma of ampulla of Vater
Hypothesis	Tumor CDX2 and MUC1 protein expression cosegregates with differential outcomes and histologic subtypes
Patients and methods	
Patients	72 (Sydney training cohort), 90 (Glasgow validation cohort), and 46 (Verona validation cohort) consecutive patients who underwent pancreaticoduodenectomy for adenocarcinoma of ampulla of Vater with curative intent (AJCC stages 1 and 2, R0 or R1; Table 1; Data Supplement)
Specimen characteristics	TMAs constructed from formalin-fixed, paraffin-embedded surgical specimens; each patient represented by 3- × 1-mm cores
Assay methods	Immunohistochemistry performed on TMAs, which were scored by two independent assessors blinded to outcomes, both of whom are specialist pancreatic pathologists
Study design	Retrospective analysis of prospectively maintained database of cohorts of consecutive patients from hospitals associated with Australian Pancreatic Cancer Genome Initiative (Sydney, Australia) for Sydney training cohort; West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, United Kingdom, for the Glasgow validation cohort; and University Hospital of Verona, Verona, Italy, for Verona validation cohort
	End point, overall survival
	Clinicopathologic features summarized in Table 1 and Data Supplement
Statistical analysis methods	Median survival estimated using Kaplan-Meier method; difference tested using log-rank test
	Clinicopathologic variables analyzed with $P < .25$ on log-rank test were entered into Cox proportional hazards multivariate analysis; models generated using backward elimination of redundant variables
	Patients were dichotomized into high/positive and low/negative:
	CDX2 expression groups based on modified H score (percentage of positive cells × intensity of staining) of 35
	MUC1 expression groups based on any staining
	There were some missing biomarker data for a small number of patients because of loss of cores on TMAs during processing; they were excluded from analyses; for Glasgow validation cohort, seven of 90 for CDX2 and one of 90 for MUC1; for Verona validation cohort, one of 46 for CDX2
Results	
Data	Clinicopathologic characteristics are comprehensively described in Table 1 and Data Supplement
Analysis and presentation	CDX2 expression associated with better prognosis on univariate analysis in both Sydney training (median survival, 172.8 *v* 69.5 months; $P = .0368$) and Glasgow validation cohorts (NA *v* 24.2 months; $P < .001$) and was borderline significant in Verona validation cohort (94.0 *v* 33.3 months; $P = .0966$)
	Absence of MUC1 expression associated with better prognosis on univariate analysis in all cohorts (Sydney training cohort: median survival, 115.5 *v* 45.0 months; $P = .0315$; Glasgow validation cohort: 67.0 *v* 20.1 months; $P = .0055$; Verona validation cohort: NA *v* 36.0; $P < .001$)
	When combining molecular and histologic subtypes, histomolecular PB phenotype (histologic PB, CDX2 negative, MUC1 positive) associated with poor prognosis compared with histomolecular non-PB (intestinal) phenotype on both univariate and multivariate analyses in Sydney training cohort (16.1 *v* 115.5 months; $P < .001$; HR, 3.40; 95% CI, 1.71 to 6.76; $P < .001$) and Glasgow validation cohort (11.9 *v* 67.0 months; $P < .001$; HR, 5.65; 95% CI, 2.77 to 11.5; $P < .001$); it was significant in only univariate analysis for Verona validation cohort (30.9 *v* 94.0 months; $P = .0088$)
Discussion	Differential CDX2 and MUC1 expression and combination of molecular and histologic criteria (histomolecular phenotype) cosegregated with prognosis in patients with adenocarcinoma of ampulla of Vater
	Histomolecular phenotyping defined two clinically relevant phenotypes of adenocarcinoma of ampulla of Vater, potentially representing two distinct diseases
	These two different phenotypes of prognosis and therapeutic responsiveness have potentially significant implications for current chemotherapeutic strategies, better interpretation of past clinical trials, and facilitation of future trial design

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; NA, not applicable (median survival not reached); PB, pancreaticobiliary; REMARK, Reporting Recommendations for Tumor Marker Prognostic Studies; TMA, tissue microarray.

one third of patients received adjuvant chemotherapy, and the chemotherapeutic agents used were variable, making interpretation difficult because of small numbers. These analyses did not reveal any association with response overall or differential response of subgroups to adjuvant therapy (data not shown).

Patients whose tumors had a histomolecular intestinal phenotype, without lymph node metastases, had an extremely favorable prognosis (approximately 85% at 5 years), and they could potentially be analogous to those with Dukes' A and Dukes' B colorectal cancers, where adjuvant chemotherapy can be avoided, presenting opportunities for decreasing treatment-associated morbidity and cost. However, patients stratified to the other two groups could be targeted aggressively, because their 5-year survival is relatively poor. Patients with histomolecular pancreaticobiliary tumors could arguably be treated like those with adenocarcinoma of the pancreas and biliary tree, and gemcitabine-based chemotherapy could be used regardless of lymph node status. On the other hand, patients with histomolecular intestinal (nonpancreaticobiliary) tumors with lymph node metastases could be treated like those with Dukes' C colorectal cancer, and FU plus leucovorin–based chemotherapy could be used. These approaches may be used to better interpret past clinical trials and better define phenotypes of therapeutic responsiveness to different adjuvant chemotherapeutic regimens. They would also better inform and more appropriately power clinical trials because approximately 40% of patients have a histomolecular intestinal phenotype carcinoma with no lymph node involvement, and any benefit would likely not be

detectable. To study a disease with such a broad range of outcomes in a clinical trial setting would require large numbers if specific patient subgroups were not enriched. Adenocarcinomas of the ampulla of Vater are a clear example where trials targeting a specific phenotypic subgroup would be most appropriate. These targeted trials would require smaller numbers to detect a larger effect, improving feasibility and decreasing cost.[33]

In conclusion, a combination of histopathologic and molecular criteria defines distinct clinically and biologically relevant histomolecular phenotypes of adenocarcinoma of the ampulla of Vater, with different outcomes and potentially different chemosensitivity profiles. Prospective assessment of this approach is encouraged to define its utility in clinical practice.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ASCO SPECIAL ARTICLE

Central Venous Catheter Care for the Patient With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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Editor's note: This is a summary of the literature that was used to inform the American Society of Clinical Oncology Clinical Practice Guideline for Central Venous Catheter Care for the Patient With Cancer and provides recommendations with brief discussions of the relevant literature for each. Evidence tables with details about the studies and meta-analyses cited are provided in Data Supplements 1 and 2 at www.asco.org/guidelines/cvc.

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ABSTRACT

Purpose
To develop an evidence-based guideline on central venous catheter (CVC) care for patients with cancer that addresses catheter type, insertion site, and placement as well as prophylaxis and management of both catheter-related infection and thrombosis.

Methods
A systematic search of MEDLINE and the Cochrane Library (1980 to July 2012) identified relevant articles published in English.

Results
The overall quality of the randomized controlled trial evidence was rated as good. There is consistency among meta-analyses and guidelines compiled by other groups as well.

Recommendations
There is insufficient evidence to recommend one CVC type or insertion site; femoral catheterization should be avoided. CVC should be placed by well-trained providers, and the use of a CVC clinical care bundle is recommended. The use of antimicrobial/antiseptic-impregnated and/or heparin-impregnated CVCs is recommended to decrease the risk of catheter-related infections for short-term CVCs, particularly in high-risk groups; more research is needed. The prophylactic use of systemic antibiotics is not recommended before insertion. Data are not sufficient to recommend for or against routine use of antibiotic flush/lock therapy; more research is needed. Before starting antibiotic therapy, cultures should be obtained. Some life-threatening infections require immediate catheter removal, but most can be treated with antimicrobial therapy while the CVC remains in place. Routine flushing with saline is recommended. Prophylactic use of warfarin or low–molecular weight heparin is not recommended, although a tissue plasminogen activator (t-PA) is recommended to restore patency to occluded catheters. CVC removal is recommended when the catheter is no longer needed or if there is a radiologically confirmed thrombosis that worsens despite anticoagulation therapy.

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INTRODUCTION

The management of the patient with cancer demands stable venous access that is used for a wide range of indications including chemotherapy, blood product and antibiotic administration, fluid resuscitation, and access to the bloodstream for clinical monitoring and microbial culturing. The use of long-term central venous catheters (CVCs) can also decrease patient anxiety associated with repeated venipunctures. The number and variety of CVCs used in oncology practices during the past 30 years have greatly increased, but the most commonly used long-term devices include: surgically implanted cuffed tunneled central venous catheters, subcutaneous implanted ports, peripherally inserted CVCs (PICCs), and percutaneous noncuffed or tunneled catheters. During the past decade, the composition of these devices has changed, the catheter size and lumen number have increased, and CVCs impregnated with anti-infective material or antibiotics and heparin have become available. A CVC care clinical bundle[1,2] is now the standard of care. The insertion and care of a CVC require a multidisciplinary approach, involving medical oncologists/hematologists, nurses, interventional radiologists, surgeons, infectious disease specialists, and often a specialized CVC care team.[3]

CVCs have a considerable potential for serious complications, which are often underappreciated.

Early complications related to CVC placement include bleeding, cardiac arrhythmia, malposition, air embolism, and pneumothorax and, rarely, injury to vessels or nerves. Late complications include infection, thrombosis, and catheter malfunction. Patients with cancer with implantable port systems were found to experience a median of 0.2 infections per 1,000 catheter-days (range, 0 to 2.7 per 1,000 catheter-days)[4] versus a risk that ranges from 1.4 to 2.2 infections per 1,000 catheter-days for subcutaneous tunneled CVCs.[5,6] Some infections can be life threatening and require immediate catheter removal, whereas others can be treated while the catheter remains in place. The incidence of CVC-associated thrombi in patients with cancer varies in different series, from 27% to 66%, when routine screening with venography is performed. Most patients with CVC thrombi are asymptomatic.[7] Reported rates of symptomatic thrombi also vary widely, from 0.3% to 28%.[7-10] Infection or thrombosis of a CVC can be an indication for removal, which can result in prolonged and costly hospitalizations and significant delays in treatment. The purpose of this guideline is to assist in care and decision making for patients with cancer who often have long-term CVCs and to identify areas of controversy, promoting future research and clinical trials. This is a new American Society of Clinical Oncology (ASCO) guideline focused on CVC care for patients with cancer.

GUIDELINE QUESTIONS

Clinical Question 1

In patients with cancer, does catheter type, insertion site, or placement technique affect complication rates?

THE BOTTOM LINE

American Society of Clinical Oncology Clinical Practice Guideline for Central Venous Catheter Care for the Patient With Cancer

Intervention

- Placement of a central venous catheter (CVC) in adult and pediatric patients with cancer and the subsequent prevention and management of catheter-related infections and thromboses

Target Audience

- Medical oncologists/hematologists, nurses, interventional radiologists, surgeons, infectious disease specialists, and specialized CVC care teams

Key Recommendations

- There is insufficient evidence to recommend a specific type of CVC or insertion site, but femoral vein insertion should be avoided, except in certain emergency situations
- CVCs should be placed by well-trained health care providers
- Use of a CVC clinical care bundle is recommended
- Use of antimicrobial/antiseptic-coated CVCs and/or heparin-impregnated CVCs has been shown to be beneficial, but the benefits and costs must be carefully considered before they can be routinely used
- Prophylactic use of systemic antibiotics is not recommended before CVC insertion
- Cultures of blood from the CVC and/or tissue at the entrance-exit sites should be obtained before initiation of antibiotic therapy; most clinically apparent exit- or entrance-site infections as well as bloodstream infections can be managed with appropriate microbial therapy, so CVC removal may not be necessary; antimicrobial agents should be optimized once the pathogens are identified; catheter removal should be considered if the infection is caused by an apparent tunnel or port-site infection, fungi, or nontuberculous mycobacteria or if there is persistent bacteremia after 48 to 72 hours of appropriate antimicrobial treatment
- Routine flushing with saline is recommended
- Prophylactic warfarin and low–molecular weight heparin have not been shown to decrease CVC-related thrombosis, so routine use is not recommended
- Tissue plasminogen activator (t-PA) is recommended to restore patency in a nonfunctioning CVC; CVC removal is recommended when the catheter is no longer needed, if there is a radiologically confirmed thrombosis that does not respond to anticoagulation therapy, or if fibrinolytic or anticoagulation therapy is contraindicated

Methods

- Systematic review and analysis of the medical literature on CVC care for patients with cancer by ASCO CVC Care Expert Panel

Additional Information

- Data Supplements, including evidence tables, and clinical tools and resources can be found at http://www.asco.org/guidelines/cvc

Clinical Question 2

What is effective prophylaxis for the prevention of catheter-related infections?

Clinical Question 3

What are effective treatments for the management of catheter-related infections?

Clinical Question 4

What is effective prophylaxis for the prevention of catheter-related thrombosis?

Clinical Question 5

What are effective treatments for the management of catheter-related occlusions?

CLINICAL PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, use of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in medical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where future research is needed

METHODS

Panel Composition

The ASCO Clinical Practice Guidelines Committee convened an Expert Panel consisting of experts in clinical medicine and research relevant to CVC care in patients with cancer, including medical and surgical oncologists and oncology nurses. Academic and community practitioners and a patient representative were also part of the Panel. The Panel members are listed in Appendix Table A1 (online only).

Literature Review and Analysis

Literature search strategy. MEDLINE (Pubmed) and the Cochrane Collaboration Library were searched with the date parameters of January 1980 through January 2012. Reference lists of related reports and review articles were scanned for additional citations. Details about the literature search and results are provided in Data Supplements 3 and 4 at www.asco.org/guidelines/cvc.

Inclusion and exclusion criteria. The systematic review conducted for this guideline included 108 randomized controlled trials (RCTs) in which adult or pediatric patients with cancer were randomly assigned to an appropriate control group or to an intervention of interest, including CVC type, placement site, or strategies to prevent or manage infection or thrombosis. Studies were included only if they had catheter type, placement site, infection, or thrombosis as a priori planned primary or secondary outcome and described a method of regular patient follow-up to ensure a consistent and identical identification of the outcomes in both study arms. Infection and/or thrombosis had to be confirmed either through objective tests (blood or imaging) and/or clinical observation. Results of meta-analyses are also reported in the Literature Review and Analysis sections pertaining to each recommendation; other guidelines, particularly those by the Centers for Disease Control and Prevention (CDC), originally published by the CDC in August 2002 and updated in 2011, and the Infectious Disease Society of America (IDSA), informed the decisions of the Panel.

Trials were excluded if they were nonrandomized reports or posthoc subgroup analyses or if only a minority of the patients studied had cancer. RCTs were also excluded if patients with CVCs were compared with patients with peripheral catheters.

Data extraction. Two reviewers independently extracted the data on basic study design, patient characteristics, interventions, study outcomes, follow-up, and measures of study quality. Any discrepancies between reviewers were resolved by consensus.

Study quality. Overall study quality was evaluated by the Jadad method. The evidence tables in Data Supplements 1 and 2 at www.asco.org/guidelines/cvc include information on randomization, blinding, allocation concealment, withdrawals, and intention-to-treat analyses. Meta-analyses were evaluated using the Oxman-Guyatt Index, in which questions must be clearly specified, target populations identified and accessed, and appropriate information obtained in an unbiased fashion.

Evidence-Based Guideline Development Process

The entire Panel met one time in person and a writing group met subsequently; additional work on the guideline was completed through a steering group and e-mail. The Panel and writing group drafted guideline recommendations and distributed writing assignments. All members of the Panel participated in the preparation of the draft guideline document, which was then disseminated for review and approval by the entire Panel. The guideline was submitted to *Journal of Clinical Oncology* for peer review. Feedback from additional external reviewers was also solicited. The content of the guideline and the manuscript was reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

Guideline Policy

The practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not recommend any particular product or course of medical treatment. Use of the practice guideline is voluntary. The guideline, evidence tables, and data supplements are available at http://www.asco.org/guidelines/cvc.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (summarized at www.asco.org/guidelinescoi).

Revision Dates

At annual intervals, the Panel co-chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel or an update committee will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revised recommendations to the Clinical Practice Guideline Committee for approval.

RESULTS

Literature Review Results and Limitations of the Literature

A total of 108 RCTs with results specific to patients with cancer (Data Supplement 1 at www.asco.org/guidelines/cvc), 25 meta-analyses or systematic reviews (Data Supplement 2 at www.asco.org/guidelines/cvc), and several existing guidelines[11-16] were identified in the search of the literature. RCTs were considered eligible for data extraction if the majority of patients had cancer. It should be noted that many of the

trials had small numbers of patients, and there was considerable heterogeneity in trial design, types of catheters used, placement techniques, and methods of evaluating end points, even among trials addressing the same question. In addition, clinical practices have changed over the years, and the Panel focused on more-recent trials whenever possible. Nonetheless, the overall quality of the evidence was rated as good, as evidenced in part by the consistency among meta-analyses and guidelines compiled by other groups.

GUIDELINE RECOMMENDATIONS

On the basis of the evidence and the expert opinion of the CVC Care Panel, the following recommendations are offered in Table 1.

Catheter Type, Insertion Site, and Placement

A CVC can be designated by its pathway to the vessel (eg, tunneled *v* nontunneled or implanted); its site of insertion (eg, subclavian, femoral, internal jugular, or PICC); or its composition, length, or special characteristic (eg, presence or absence of a cuff; impregnation with heparin, antibiotics, or antiseptics; single or multiple lumens). When selecting the proper CVC, factors to consider are the purpose, the expected duration of the catheter, who will maintain the device, and patient preference. The use of a CVC should be considered for patients with cancer (adults and children) with limited peripheral venous access, for those receiving regimens that require prolonged or continuous intravenous (IV) infusions of multiple chemotherapeutic or supportive care agents, for those requiring repeated blood sampling or clinical monitoring, and for those expected to receive a vesicant as

Table 1. ASCO Recommendations for CVC Care

Clinical Question	Recommendation
1. In patients with cancer, does catheter type, insertion site, or placement affect complication rates?	1.1. There is insufficient evidence to recommend one type of CVC routinely for all patients with cancer; the choice of catheter should be influenced by the expected duration of use, chemotherapy regimens, and patient ability to provide care; the minimum number of lumens essential for the management of the patient is recommended; these issues should be discussed with the patient
	1.2. There is insufficient evidence to recommend one insertion site or approach (left sided or right sided) for tunneled CVCs for patients with cancer; individual risks and benefits (comfort, security, maintenance of asepsis) of the catheter site should be considered; the Panel recommends that CVC insertion into the femoral vein be avoided because of increased infection risks and concerns about thrombosis, except in certain emergency situations
	1.3. Most CVC placement in patients with cancer is performed as an elective procedure; although image-guided insertion (eg, ultrasound guided, fluoroscopy) of CVCs is recommended, well-trained providers who use the landmark method regularly (eg, for subclavian or internal jugular) may have high rate of success and low incidence of acute and/or chronic complications
2. What is effective prophylaxis for the prevention of catheter-related infections?	2.1. CVC care clinical bundle (including hand hygiene, maximal barrier precautions, chlorhexidine skin antisepsis during catheter insertion, optimal catheter site selection, and assessment of CVC necessity) is recommended for placement and maintenance of all CVCs to prevent infections; there is no evidence that particular dressing types or more frequent IV set and/or dressing changes decrease risk of infection; use of topical antibiotic ointment or cream on insertion sites is not recommended because of potential to promote fungal infections and resistance to antimicrobials; scheduled guidewire exchange of CVC may be associated with greater risk of infection versus catheter replacement at new vascular site; thus, guidewire exchange is not routinely recommended, unless access options are limited
	2.2. Use of antimicrobial/antiseptic-impregnated or -coated CVCs (CH-SS or minocycline/rifampin) and/or heparin-impregnated catheters is recommended to decrease risk of catheter-related infections for short-term CVCs, particularly in high-risk groups such as bone marrow transplantation recipients or patients with leukemia; however, relative benefit and increased cost must be carefully considered before they are routinely used
	2.3. Prophylactic use of systemic antibiotics (IV or oral) before insertion of long-term CVCs is not recommended
	2.4. There are conflicting data about the relative value of prophylactic heparin with saline flushes to prevent catheter-associated bloodstream infections or thrombosis; data are not sufficient to recommend for or against routine use of antibiotic-flush/antibiotic-lock therapy
3. What are effective treatments for the management of catheter-related infections?	3.1. Cultures of blood from the catheter and when appropriate of soft tissues at entrance-exit sites or tunnel should be obtained before initiation of antibiotic therapy; most exit- or entrance-site infections can be treated successfully with appropriate antimicrobial therapy without the need for catheter removal, although removal is usually needed for clinically apparent tunnel or port-site infections; antimicrobial agents should be optimized once pathogens are identified and antibiotic susceptibilities defined
4. What is effective prophylaxis for the prevention of catheter-related thrombosis?	4.1. Use of systemic anticoagulation (warfarin, LMWH, UFH) has not been shown to decrease incidence of catheter-associated thrombosis; therefore, routine prophylaxis with anticoagulants is not recommended for patients with cancer with CVCs; routine flushing with saline of the CVC to prevent fibrin buildup is recommended
	4.2. Data are insufficient to recommend routine use of urokinase (not available in the United States) and/or other thrombolytics to prevent catheter occlusion
5. What are effective treatments for the management of occluded catheters?	5.1. Instillation of 2-mg t-PA is recommended to restore patency and preserve catheter function
	5.2. Although it is appropriate to try to clear thrombosis with the CVC in place, if there is radiologically confirmed thrombosis that does not respond to fibrinolytic therapy or if fibrinolytic or anticoagulation therapy is contraindicated, catheter removal is recommended; prolonged retention of unneeded CVCs can lead to significant problems associated with thrombosis and fibrosis; 3 to 6 months of anticoagulant therapy with LMWH or LMWH followed by warfarin (INR, 2.0 to 3.0) is recommended for treatment of symptomatic CVC thrombosis, with duration depending on clinical issues in individual patients

Abbreviations: ASCO, American Society of Clinical Oncology; CH-SS, chlorhexidine and silver sulfadiazine; CVC, central venous catheter; INR, international normalized ratio; IV, intravenous; LMWH, low–molecular weight heparin; t-PA, tissue plasminogen activator; UFH, unfractionated heparin.

part of their treatment regimen. It should be noted, however, that many regimens containing vesicants can be administered safely to patients with good peripheral venous access by skilled infusion nurses. Patient education about types of CVCs facilitates an informed decision before catheter placement, because the decision about the type of catheter should involve both the health care provider and the patient (see Patient and Clinician Communication section). A table of CVC types and risks of infection is provided in Data Supplement 5 at www.asco.org/guidelines/cvc.

Clinical Question 1

In patients with cancer, does catheter type, insertion site, or placement affect complication rates?

Recommendation 1.1. There is insufficient evidence to recommend one type of CVC routinely for all patients with cancer. The choice of catheter should be influenced by the expected duration of use, the chemotherapy regimen, and the patient's ability to provide care. The minimum number of lumens essential for the management of the patient is recommended. These issues should be discussed with the patient.

Literature review and analysis. Ten RCTs[17-26] and three meta-analyses[6,27,28] addressed these issues. They supported the conclusions that single- or double-lumen (*v* triple) CVCs should be used whenever feasible; and that, for a patient who requires more intensive therapy (ie, hematopoietic cell transplantation recipient, patient with acute leukemia), a subcutaneous port is often not adequate to meet all the patient's clinical needs. In one meta-analysis,[6] the authors reviewed 200 prospective studies in adult patients. Catheter types were compared using the mean rates of intravascular device (IVD) –related bloodstream infections (BSIs) per 100 IVDs (%) and per 1,000 IVD-days. Point incidence rates of IVD-associated BSIs were lowest for peripheral IV catheters (0.5 per 1,000 IVD-days) and were much higher for short-term, noncuffed, and non–antimicrobial-impregnated CVCs (2.7 per 1,000 IVD-days). Surgically implanted long-term cuffed and tunneled central venous devices resulted in an intermediate infection risk (1.6 per 1,000 IVD-days). PICCs for patients who were hospitalized seemed to pose a substantial risk of infection (2.4%; 2.1 per 1,000 IVD-days), but when assessed just for patients who received both inpatient and outpatient care, the risk of infection was much lower (1.1 per 1,000 IVD-days). The published data do not provide a specific recommendation that could apply to all patients with cancer because of the heterogeneity of the patient populations, variability of the severity of patient illness, different protocols for insertion and site care, and multiple different devices that were tested. Thus, it is critical to carefully consider the patient's present and future needs in making the decision about catheter type.

Recommendation 1.2. There is insufficient evidence to recommend one insertion site or approach (left sided or right sided) for tunneled CVCs for patients with cancer. Individual risks and benefits (comfort, security, and maintenance of asepsis) of the catheter site should be considered. The Panel recommends that CVC insertion into the femoral vein be avoided because of increased infection risks and concerns about thrombosis, except in certain emergency situations.

Literature review and analysis. Evidence from six RCTs[21,29-33] and one meta-analysis[34] indicated that there was no compelling evidence for one insertion site or approach (left sided or right sided). No differences were found for early complication rate among three groups (internal jugular, 0%; 95% CI, 0.0% to 2.7%; subclavian, 0%; 95% CI, 0.0% to 2.7%; cephalic, 1.5%; 95% CI, 0.1% to 5.3%).[29] Four of the RCTs[21,31-33] evaluated subcutaneous tunneled CVCs for patients with malignancies, and taken together, the results of the studies show that subcutaneous tunneling decreases the rate of short- and long-term complications. The CDC guideline[14] and one RCT[35] present data that femoral vein CVCs have relatively high bacterial colonization rates when used in adults and an equivalent infection rate in children, and another meta-analysis provides data that a femoral placement can increase thrombosis[36]; thus, femoral vein insertion should be avoided when other sites are available.

Recommendation 1.3. Most CVC placement in patients with cancer is performed as an elective procedure. Although image-guided insertion (eg, ultrasound guided, fluoroscopy) of CVCs is recommended, well-trained providers who use the landmark method regularly (eg, for subclavian or internal jugular) may have a high rate of success and a low incidence of acute and/or chronic complications.

Literature review and analysis. Four RCTs[37-40] and three meta-analyses[41-43] specifically addressed the effectiveness of teams who used image-guided versus landmark-guided CVC placement (eg, subclavian or internal jugular). Using two-dimensional or Doppler ultrasound may achieve lower complication rates.[37] In one RCT, although there were no significant differences, in secondary measures (such as pneumothorax, arterial puncture, hematoma), there was 14% misplacement in the blind arm versus only 1% misplacement in the image-guided arm ($P = .001$). However, another RCT[38] found that real-time Doppler guidance of subclavian vein catheterization is highly operator dependent and did not increase the success rate or decrease the complication rate of subclavian vein catheterization when compared with the standard technique in high-risk patients, nor was it more useful than the standard technique as a salvage technique after a previous failure of catheterization. Another small RCT[39] found that ultrasound techniques did not influence the rate of complication or failure of subclavian vein catheterizations. The authors reported a 12% failure rate (n = 51) in the ultrasound group and 12% failure rate (n = 49) in the control group. A final RCT[40] concluded that the surface landmark technique was not as reliable as IV electrocardiography-guided catheter tip placement (satisfactory placement for 16 of 30 patients *v* 30 of 30 patients, respectively).

In meta-analyses,[41-43] it was concluded that two-dimensional ultrasound is significantly better than the landmark method. Not all the patients in these meta-analyses had cancer, and thus, there was significant heterogeneity of study results. However, in another meta-analysis,[41] a subgroup analysis suggested improved outcomes for patients with cancer with image-guided CVC insertion.

Infection

The CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections[14] and the IDSA 2009 Update of the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection[44] conclude that experienced, educated health care workers or dedicated CVC teams are critical for infection prophylaxis for CVCs in patients with cancer. The CDC and IDSA guidelines were written for all patients but provide specific recommendations regarding diagnosis and management of infection for patients with cancer as well. Two RCTs focusing on patients with cancers[45,46] reported that catheter-related infections are largely preventable and that education for all providers and systematic individualized, supervised patient and caregiver education are effective and affordable and decrease infection rates.

Catheter-related infections can be grouped into one of three categories: one, localized entrance- or exit-site infections; two, tunnel and/or port-pocket infections; and three, catheter-associated BSIs (catheter-related BSIs). The pathogens that cause catheter-associated infections have changed during the past decades, influenced by changing catheter materials, antimicrobial impregnation of the catheters, sites of catheter placement, and the antimicrobial selection that occurs as a result of changing antibiotic prescribing habits. More detailed information is available at Definitions of Infections Associated With CVCs and Treatment, provided in Data Supplement 6 at www.asco-.org/guidelines/cvc. In general, entrance- or exit-site infections are associated with a low incidence of BSIs. However, tunnel or port-site catheter BSIs are not uncommon and can be a significant cause of morbidity. The consequences of catheter-related infections depend on several factors such as the type of CVC, the catheter placement location, and the patient's performance status, including associated myelo/immunosuppression. Patients with cancer with implantable port systems were found to experience a median of 0.2 infections per 1,000 catheter-days (range, 0 to 2.7 per 1,000 catheter-days)[4] versus a risk that ranges from 1.4 to 2.2 infections per 1,000 catheter-days for subcutaneous tunneled CVCs.[5,6] However, this difference may be artifactual, because patients who receive implantable subcutaneous ports usually receive much less intensive cancer therapy. The duration of antimicrobial therapy for the treatment of catheter-associated infections ranges from 7 to 21 days, and success rates have ranged from 60% to 91%.[47] It is important to note that both duration of treatment and treatment success are highly dependent on the organism(s) responsible for the infection, the need for catheter or subcutaneous port removal, and the patient's underlying neutrophil count. Early catheter removal is critical for some infections, whereas premature or unnecessary catheter removal may interrupt treatment and increase patient discomfort, anxiety, and cost because of the need for placement of another catheter.

Clinical Question 2

What is effective prophylaxis for the prevention of catheter-related infections?

Recommendation 2.1. A CVC care clinical bundle (including hand hygiene, maximal barrier precautions, chlorhexidine skin antisepsis during catheter insertion, optimal catheter site selection, and assessment of CVC necessity) is recommended for the placement and maintenance of all CVCs to prevent infections (Table 2). There is no evidence that particular dressing types or more frequent IV set and/or dressing changes decrease the risk of infection. The use of topical antibiotic ointment or cream on insertion sites is not recommended because of the potential to promote fungal infections and resistance to antimicrobials. A scheduled guidewire exchange of CVCs may be associated with a greater risk of infection compared with catheter replacement at a new vascular site, and thus, guidewire exchange is not routinely recommended unless access options are limited.

Literature review and analysis. CVC clinical care bundles have been validated as a highly effective approach to decrease catheter-related BSIs.[1,2,16,48,49] As has been shown in many RCTs, including three performed in patients with cancer, and in meta-analyses, antiseptic chlorhexidine-based preparations used at the time of insertion decrease the incidence of CVC-related infections by 40% to 50% compared with povidone-iodine solutions.[50-53] Of note, one meta-analysis conducted in 2006[53] also assessed the effect of an antiseptic chlorhexidine-impregnated dressing on the risk of vascular and epidural catheter bacterial colonization and infection. The chlorhexidine-impregnated dressing substantially reduced the risk of intravascular catheter or exit-site bacterial colonization (14.8% *v* 26.9%; odds ratio [OR], 0.47; $P < .001$). In contrast, in eight RCTs,[54-61] patients with entrance- or exit-site dressings, combined with antibiotic ointments applied at the insertion site, experienced a higher incidence of catheter-related infections than those patients for whom no antibiotic ointment or cream was used.

Several RCTs, systematic reviews, and meta-analyses conducted among patients with cancer have addressed the frequency of catheter dressing changes, replacement of administration sets, and replacement of catheters using a vascular guidewire.[14,61-65] Scheduled guidewire exchanges of CVCs failed to reduce infection rates compared with replacement at a new site, and indeed, the routine replacement of catheters that are functioning well and do not seem to be infected is not recommended.[64]

Recommendation 2.2. The use of antimicrobial/antiseptic-impregnated or -coated CVCs (chlorhexidine and silver sulfadiazine [CH-SS] or minocycline/rifampin) and/or heparin-impregnated catheters is recommended to decrease the risk of catheter-related infections for short-term CVCs, particularly in high-risk groups such as bone marrow transplantation recipients or patients with leukemia. However, the relative benefit and increased cost must be carefully considered before they are routinely used.

Literature review and analysis. Regarding CVCs impregnated with CH-SS, although the data are mixed, evidence from five RCTs[66-70] and two meta-analyses[71,72] indicates that antimicrobial/

Table 2. CVC Clinical Care Management Bundle

Component	Criteria
Hand hygiene	Every person entering the room during the insertion procedure should perform hand hygiene
Maximal barrier precautions upon insertion	Sterile drape extends from head to toe; all health care providers participating in the procedure employ mask, cap, sterile gown, and sterile gloves
Chlorhexidine skin antisepsis	Skin at the insertion site should be scrubbed with 2% chlorhexidine for 30 seconds and allowed to dry for at least 30 seconds
Optimal catheter site selection	Subclavian vein is the preferred site for nontunneled catheters; avoid femoral site if possible
Assessment of CVC necessity	Prompt removal of CVC line after completion of therapy unless clinical circumstances suggest that further infusional therapy is likely to be necessary in the future

NOTE. Content adapted.[1,14,48]
Abbreviation: CVC, central venous catheter.

antiseptic-impregnated catheters and cuffs that are coated externally with CH-SS reduce catheter-related BSIs and catheter-related colonization, although there is some evidence to the contrary; one meta-analysis[72] included studies with methodologic flaws, whereas the nonsignificant findings in three RCTs may have resulted from the development of newer generations of coated catheters.

Regarding CVCs impregnated with minocycline/rifampin, in one large RCT,[73] patients with cancer randomly assigned to long-term, nontunneled silicone CVCs impregnated with minocycline and rifampin had lower rates of catheter-related BSIs versus those randomly assigned to nonimpregnated catheters (0.25 *v* 1.28 infections per 1,000 catheter-days, respectively; $P = .003$). In another RCT,[74] BSIs were four times less likely to originate from impregnated silicone catheters. In a meta-analysis[75] of trials not restricted to patients with cancer, rifampicin/minocycline-impregnated CVCs were associated with fewer catheter-related BSIs compared with catheters not impregnated with rifampicin/minocycline.

With regard to CVCs impregnated with heparin, intraluminal fibrin deposition may contribute to the development of infection, and hence, a CVC-impregnated with heparin has the potential to reduce catheter-related infections.[76] In one RCT of patients with cancer, catheter-related BSIs occurred in 2.5% of patients (three of 120 catheters) with heparin-coated catheters with saline infusion (0.9 events per 1,000 days) versus 9.1% of patients (11 of 120 catheters) with noncoated catheters flushed with unfractionated heparin in the control group (3.5 events per 1,000 days; $P = .027$).[76]

The use of antimicrobial-impregnated CVCs remains somewhat controversial because of cost. Catheters impregnated with CH-SS or minocycline/rifampin (and heparin) are more expensive than standard catheters, although it has been suggested that such catheters could be cost effective in higher-risk patients. It should be noted that a majority of these studies were conducted in patients with short-term CVCs.

Recommendation 2.3. The prophylactic use of systemic antibiotics (IV or oral) before insertion of a long-term CVC is not recommended.

Literature review and analysis. The routine use of systemic antibiotics (IV or oral) before the insertion of a CVC to prevent infection is not recommended.[44] This recommendation is supported specifically for patients with cancer in one RCT[77] when the CVC care bundle was used and in four RCTs[78-81] where prophylactic systemic antibiotics, including vancomycin, did not significantly reduce catheter-related sepsis in patients with cancer. Two small RCTs,[82,83] with methodologic issues, were inconclusive.

In a Cochrane review of nine RCTs,[84] CVC tunnel infections were not reduced by the use of prophylactic IV antibiotics before catheter insertion (OR, 0.42; 95% CI, 0.13 to 1.31), although flushing the CVC lumens with antibiotics and heparin seemed to decrease the incidence of Gram-positive infections (OR, 0.43; 95% CI, 0.21 to 0.87). This seemingly positive meta-analysis should be considered carefully before it is translated to most patients with cancer because of the small number of studies and patients.

Recommendation 2.4. There are conflicting data about the relative value of prophylactic heparin with saline flushes to prevent catheter-associated BSIs or thrombosis. Data are not sufficient to recommend for or against the routine use of antibiotic-flush/antibiotic-lock therapy.

Literature review and analysis. Numerous flushing protocols exist, often determined by the manufacturer, which use different volumes and concentrations of heparin, saline, or tissue plasminogen activator (t-PA; or other similar agents) and different frequencies for catheter flushing. Antimicrobial/antiseptic-coated CVCs or heparin-impregnated CVCs are recommended, but conflicting data from one RCT and a meta-analysis[85,86] suggest that the evidence supporting the use of prophylactic heparin with saline flushes is inconclusive, and definitive randomized comparisons have not been performed. A randomized trial[87] in the intensive care unit setting evaluating short-term catheter placement did not show a difference between heparin or saline flushes in the rate of catheter thrombosis or catheter-related BSIs. There is a theoretic concern about the clinical syndrome of heparin-associated thrombocytopenia with heparin flushes, although the incidence of this complication has not been determined and seems to be low. The issue of antibiotic flushing and/or antibiotic lock techniques continues to be controversial. The CDC guideline[14] is in favor of these techniques only if the patient is at risk because of a history of previous infections. This is supported by seven RCTs, which reported a significant decrease in catheter-related BSIs or an increase in the time to first episode of catheter-related BSI when antibiotic flush or bacteriostatic saline flushes were used.[85,88-93] In addition, two other older small RCTs[94,95] concluded that vancomycin locks or catheter flushes may prevent bacteremia by vancomycin-susceptible organisms in non-neutropenic pediatric patients. This practice must be weighed against the risk that routine use of vancomycin may result in the selection of resistant bacteria. Alternately, two other RCTs[78,96] reported that the addition of vancomycin to heparin CVC flush solution did not reduce bacteremia with vancomycin-susceptible organisms.

Another meta-analysis[5] of seven prospective, randomized trials ($n = 463$) compared a vancomycin-heparin lock or flush solution with heparin alone for prevention of BSI. Five of these seven studies were conducted among patients with cancer. The summary risk ratio supporting the use of vancomycin-heparin lock solutions for the prevention of IVD-associated BSIs was 0.49 (95% CI, 0.26 to 0.95; $P = 03$). When vancomycin was instilled in the catheter for a defined period, rather than simply flushing it directly through the catheter, the benefit was greater, with a risk ratio of 0.34 (95% CI, 0.12 to 0.98; $P = .04$). The results of the test for heterogeneity were statistically significant, although heterogeneity was no longer present when one of the studies was removed. Thus, clinicians must be cautious in the interpretation of these data.

Two RCTs addressed the use of urokinase flushes/locks or urokinase-heparin flushes/locks in patients with cancer.[97,98] Because urokinase is no longer available in the United States, this intervention is no longer applicable in the United States.

Management of Clinically Established Catheter-Related Infection

Determining the source of BSI is often challenging in patients with long-term indwelling CVCs. A helpful diagnostic tool for attempting to diagnose a catheter-related BSI is the differential time to positivity of blood cultures drawn simultaneously through the catheter and a peripheral vein. A blood culture drawn from the CVC that becomes positive at least 120 minutes earlier than simultaneously drawn peripheral vein blood indicates that the catheter is the likely source of infection.[99] Many approaches to quantify the number of organisms cultured from each site have been proposed. Although not

specific to patients with cancer, there are recommendations for culturing and treatment in the IDSA 2009 Update of the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection[44] (pocket card can be found at http://www.idsociety.org/IDSA_Practice_Guidelines/including). The use of antimicrobial agents in patients with cancer and/or neutropenia are also clearly addressed in the IDSA 2010 Update of the Clinical Practice Guideline for the use of Antimicrobial Agents in Neutropenic Patients with Cancer.[100] Information on the management of febrile neutropenia in the outpatient setting can be found at www.asco.org/guidelines/outpatientfn.

Specific therapy with standard antimicrobial agents should be initiated as soon as possible. Catheter-related BSIs are most commonly caused by coagulase-negative staphylococci, *Staphylococcus aureus*, and *Candida* species and less commonly with *Bacillus* species, *Corynebacterium jeikeium*, enterococci (including vancomycin resistant), rapidly growing mycobacteria, and nonlactose fermenting Gram-negative bacilli.[44] Many of these pathogens are organisms that frequently colonize the skin.

Most BSIs that occur in patients with cancer can be treated effectively without catheter removal. Clinical experience suggests that most bloodstream infections that occur among patients with cancer may not actually originate from or involve the catheter. That said, fungemias or bacteremias with *Bacillus* species, *C jeikeium*, *S aureus*, *P aeruginosa*, or *Stenotrophomonas maltophilia* and nontuburculous mycobacteria (eg, *Mycobacterium chelonei*, *M fortuitum*, *M mucogenicum*, *M abscessus*) often persist despite appropriate antibiotics and then require catheter removal. Catheter removal should also be considered when blood cultures remain positive after 48 hours of antibiotic treatment if no other site of infection has been identified or if bacteremia recurs shortly after completion of a course of antibiotics.

In some patients, catheter removal is not advisable because of platelet transfusion refractory thrombocytopenia and hemorrhagic hazards associated with reimplantation or the absence of other vascular access sites. In these complex cases where the catheter is to be retained, the clinician may find it prudent to prolong the duration of IV antimicrobial therapy.

Clinical Question 3

What are effective treatments for the management of catheter-related infections?

Recommendation 3.1. Cultures of blood from the catheter and when appropriate of soft tissues at the entrance-exit sites or tunnel should be obtained before the initiation of antibiotic therapy. Most exit- or entrance-site infections can be treated successfully with appropriate antimicrobial therapy without the need for catheter removal, although removal is usually needed for clinically apparent tunnel or port-site infections. Antimicrobial agents should be optimized once the pathogens are identified and antibiotic susceptibilities defined.

Immediate catheter removal is recommended for BSIs caused by fungi and nontuburculous mycobacteria (eg, *M chelonei*, *M fortuitum*, *M mucogenicum*, *M abscessus*). BSIs caused by *Bacillus* species, *C jeikeium*, *S aureus*, *P aeruginosa*, *S maltophilis*, and vancomycin-resistant enterocci may be difficult to eradicate with antimicrobial therapy alone, and early catheter removal should be considered. Catheter removal is also recommended for patients with an apparent tunnel or port-site infection, persistent bacteremia after 48 to 72 hours of appropriate antimicrobial treatment in the absence of other obvious sites or sources of infection, infective endocarditis or peripheral embolization, presence of local catheter-associated complications not responsive to treatment, or relapse of infection with the same pathogen after the completion of an appropriate course of antibiotics.

Literature review and analysis. There are five RCTs[95,101-104] specifically focused on treatment options for patients with cancer with catheter-related infections. Once the diagnosis of a catheter-related BSI is established or suspected (more information about culturing is available in Data Supplement 7 at www.asco.org/guidelines/cvc), decisions about the duration and type of antimicrobial therapy and catheter removal should be made depending on the patient's disease status, presence of myelosuppression, previous antibiotic exposure, the isolated pathogen, and the type of catheter. In hemodynamically stable patients, depending on the pathogen and in the absence of signs of metastatic infection and/or tunnel or port-site infection, many catheter-related BSIs can be effectively treated without catheter removal, assuming the patient clinically improves, and blood cultures become negative within 48 to 72 hours after antibiotic initiation. Most catheter-related BSIs caused by coagulase-negative *Staphylococcus* can be successfully managed with the catheter in place. These recommendations are consistent with guidelines from other groups, including the IDSA. In contrast, tunnel and port-pocket infections generally require prompt catheter removal coupled with modification of empiric antibiotics based on cultures and the antibiotic susceptibilities of the recovered pathogens.

The duration of systemic antimicrobial therapy after a catheter-related BSI is documented depends on several factors including: catheter removal or retention, response to antimicrobial therapy within the first 48 to 72 hours (resolution of fever and bacteremia), and the development of other complications (embolic tissue infection, septic thrombosis, or endocarditis). In general, for organisms other than coagulase-negative *Staphylococci*, a 14-day course of systemic antimicrobial therapy is adequate, assuming a response to antimicrobial therapy within 48 to 72 hours and the absence of a deep-tissue infection, even in a patient with neutropenia. However, a recent study suggested that catheter-related BSIs resulting from *S aureus* in patients with cancer (including neutropenic patients) may improve with durations of therapy that are longer than 2 weeks because of the increased risk of complications with shorter treatment courses.[105] Catheter-related BSIs resulting from any pathogen that are complicated by disseminated or deep infection require at least 4 to 6 weeks of antimicrobial therapy.[44,100]

Thrombosis

In 2007, ASCO published a guideline addressing the many issues related to venous thromboembolism in patients with cancer: Clinical Practice Guideline Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer.[106] CVC-associated thrombosis was not considered in that guideline. This guideline is currently being updated. Thrombosis associated with a CVC can involve the catheter tip, the length of the catheter, or the catheterized vessel in the upper limb, with or without involvement of the central vasculature of the neck or mediastinum.

The incidence of catheter-related thrombosis (symptomatic and asymptomatic) in patients with cancer varies considerably, ranging as high as 27% to 66% in adults[7] and 50% in children.[107] The variation is in part related to the different techniques (eg, venography, ultrasonagraphy) used to assess catheter-associated clots, differing definitions

of thrombosis, and varying study designs. In one systematic review, the rates of symptomatic thrombosis were between 0.3% and 28.6%,[7] whereas another review found that on average, 12% of CVC thrombosis events were symptomatic.[8] In more recent years, however, lower rates of symptomatic CVC-related venous thrombosis in the range of 4% to 8% have been reported.[10,108,109] The reasons for this decrease are unclear, but it has been suggested that improvement in catheter materials, better insertion practices, and better catheter maintenance are contributory. Malpositioning of the catheter tip can cause difficulties with blood withdrawal and contribute to catheter occlusion. A catheter that is too short increases the risk of thrombosis; therefore, proper insertion technique and confirmation of catheter tip placement are important. Clinical symptoms of CVC-related thrombosis include edema, pain, and erythema of the affected limb, which can develop acutely or over a more prolonged period of time. With upper-extremity catheters, there may be swelling of the neck, supraclavicular area, or face. Often, problems with catheter function can lead to ultrasound or radiographic evaluations, which identify catheter-associated clots.

Clinical Question 4

What is effective prophylaxis for the prevention of catheter-related thrombosis?

Recommendation 4.1. The use of systemic anticoagulation (warfarin, low –molecular weight heparin [LMWH], or unfractionated heparin) has not been shown to decrease the incidence of catheter-associated thrombosis, and therefore, routine prophylaxis with anticoagulants is not recommended for patients with cancer with CVCs. Routine flushing with saline of the CVC to prevent fibrin buildup is recommended.

Literature review and analysis. Older studies produced conflicting conclusions regarding the efficacy of routine primary thromboprophylaxis in patients with cancer. Two small RCTs[110,111] evaluated the use of low-dose warfarin and LMWH to prevent catheter-related thrombosis. Although in retrospect, there were many methodologic issues with the first study,[110] the use of low-dose warfarin became common in some clinical practices. It was noted subsequently that the prothrombin time could be prolonged excessively in some patients because of interactions with chemotherapy drugs.[112]

More recently, 10 randomized trials, three systematic reviews, and one meta-analsyis have addressed the routine use of thromboprophylaxis using a variety of different anticoagulants in a variety of different populations of patients with cancer.[113-126] Details of these articles are provided in the evidence tables in Data Supplements 1 and 2 at www.asco.org/guidelines/cvc. The use of anticoagulants did not increase the risk of bleeding, although bleeding certainly remains a concern in patients receiving intensely myelosuppressive therapy. More importantly, the systematic reviews and meta-analysis did not show a decrease in the incidence of symptomatic CVC-related thrombosis, and hence, the systemic administration of anticoagulants to prevent CVC-associated thromboses is not recommended.

There are a number of reasons that may explain the differences in event rates of contemporary compared with earlier studies. First, earlier trials were not double blinded and may have overestimated the treatment effects because of possible biases in diagnosis. Second, improvements in biocompatibility, insertion, and maintenance techniques for CVCs have helped to lower thrombosis rate in recent years, necessitating large trials to detect differences. Third, the patient populations may have been different in the earlier trials. A number of new antithrombotic agents are undergoing clinical investigation or are in the pipeline, but more highly powered RCTs of better design are needed to define whether specific subgroups of patients with cancer might benefit from receiving thromboprophylaxis.

A special note is warranted for Factor V Leiden. A meta- analysis[127] of 10 studies was published on 1,000 patients with cancer with Factor V Leiden and the G20210A prothrombin mutation (PTM). The pooled OR for CVC-related thrombosis was 4.6 (95% CI, 2.6 to 8.1) in patients with Factor V Leiden compared with those without. The pooled OR for CVC-related thrombosis was 4.9 (95% CI, 1.7 to 14.3) in patients with PTM. The estimated attributable risk of CVC-related thrombosis was 13.1% for Factor V Leiden. They concluded that the presence of Factor V Leiden and PTM is associated with CVC-related thrombosis. However, Factor V Leiden and the prothrombin gene mutation were not associated with an increased risk of catheter-associated thrombosis in another study.[128] The study also described an increased risk of catheter-associated thrombosis with elevated homocysteine levels. Overall, there is no clear consensus at this time regarding the role of either inherited or acquired thrombophilic states in the pathogenesis of catheter-associated thrombosis, nor is there a clear recommendation on the use of prophylactic measures in this population.

Recommendation 4.2. Data are insufficient to recommend routine use of urokinase (not currently available in the United States) and/or other thrombolytics to prevent catheter occlusion.

Literature review and analysis. Three RCTs have evaluated methods to decrease the risk of CVC occlusion by flushing with urokinase in a variety of patient populations, and the conclusions are mixed. In two of the three studies,[129,130] patients receiving urokinase had fewer occlusive events (23% *v* 31%; $P = .02$ and 4% *v* 16%; $P < .05$). In contrast, another study[131] did not report any benefit of prophylactic urokinase in a trial of 100 patients undergoing bone marrow transplantation (including a large number of patients undergoing autologous transplantation for breast cancer) or receiving high-dose chemotherapy for hematologic malignancies. The incidence of catheter-related thrombosis was also similar in both groups, with 16% of the heparin group and 19% of the urokinase group developing a symptomatic upper-extremity deep venous thrombosis. One of the studies was closed early because of withdrawal of urokinase in the United States; nonetheless, it was determined that there were no significant differences in occlusive events with urokinase versus heparin instillation.[129]

It is not clear why the incidence of catheter occlusion was different among the three RCTs, although the patient populations varied, and the definition and diagnosis of catheter occlusion differed. On the basis of both the lack of solid evidence and the unavailability of the agent in the United States, it is not possible for the Panel to recommend urokinase prophylaxis to prevent catheter occlusion.

Two other RCTs examined alternative interventions to prevent thrombotic events. One study[132] found that ionic implantation of silicone chronic venous access devices did not alter thrombotic complications in a double-blinded, randomized clinical trial, whereas another small, and probably underpowered, study[133] suggested that a novel silver-coated CVC did not affect the rate of CVC-related thrombosis.

Management of Catheter-Related Occlusion

Clinical Question 5

What are effective treatments for the management of catheter-related occlusions?

Recommendation 5.1. The instillation of 2-mg t-PA is recommended to restore patency and preserve catheter function.

Literature review and analysis. Four RCTs[134-137] have evaluated methods of restoring line patency using fibrinolytic therapy (alteplase [t-PA], reteplase, or tenecteplace), urokinase with t-PA, or urokinase with heparin (urokinase unavailable in the United States) for catheter occlusions. Most cancer centers have standard policies and procedures to treat asymptomatic CVC occlusions[138] with thrombolytic drugs. Although more studies are needed to establish a consensus for treatment of asymptomatic CVC-related thrombosis,[139] most are often diagnosed incidentally by cancer staging studies. Current data suggest that the treatment of incidental thrombi should be the same as treatment of symptomatic thrombi. These issues will be addressed in more detail in the forthcoming update (manuscript submitted, Lyman et al: Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update).

Recommendation 5.2. Although it is appropriate to try to clear a thrombosis with the CVC in place, if there is radiologically confirmed thrombosis that does not respond to fibrinolytic therapy or if fibrinolytic or anticoagulation therapy is contraindicated, catheter removal is recommended. Prolonged retention of an unneeded CVC can lead to significant problems associated with thrombosis and fibrosis. Three to 6 months of anticoagulant therapy with LMWH or LMWH followed by warfarin (international normalized ratio, 2.0 to 3.0) is recommended for the treatment of symptomatic CVC thrombosis, with the duration depending on clinical issues in individual patients.

Literature review and analysis. There are no randomized trials of anticoagulant therapy in patients with acute symptomatic CVC thrombosis. The natural history of acute CVC thrombosis is unclear. Although pulmonary embolism can occur,[140] the incidence is less frequent than that of proximal deep vein thrombosis of the leg. Treatment of this condition is based on extrapolation of the results of acute deep leg vein thrombosis. The duration of anticoagulation therapy is unclear, but 3 to 6 months seems reasonable. It is possible (even likely) that the duration of anticoagulation can be shorter if the catheter has been removed. Additional clinical issues, such as the planned administration of intensive chemotherapy that will produce thrombocytopenia, should be considered in individual patients.

The timing of the removal of a CVC because of a CVC-related thrombosis is unclear. It is the expert opinion of the CVC Care Panel that it may not always be necessary to remove the catheter in patients with CVC-associated thrombosis. One alternative is to keep the CVC in place and to add systemic anticoagulants, but there are no RCTs addressing this issue. For patients with deep vein thrombi for whom there are contraindications for anticoagulation, such as those with active bleeding, platelet count $< 50{,}000/\mu L$, or recent CNS bleeding or surgery, catheter removal is recommended, and anticoagulation therapy should be initiated if and/or when it becomes possible. Patients with cancer who have had their CVCs removed and then replaced without anticoagulation often experience recurrent thrombosis, but this has not been sufficiently studied. An important issue that needs to be studied is where to put the next CVC. Future research questions should include analyses of the development of postphlebitic syndrome, the importance and value of testing for thombophilia and inherited disorders such as Factor V Leiden in patients who experience thromboses, and the management of small pericatheter clots detected by imaging studies in otherwise asymptomatic patients. Other ideas for future research on CVC care for patients with cancer are available in Data Supplement 8 at www.asco.org/guidelines.cvc.

PATIENT AND CLINICIAN COMMUNICATION

Adequate vascular access is critical for the patient with cancer and should be included in the patient assessment when making treatment decisions. Many CVCs are available; however, there is no evidence-based guideline for the selection of a particular CVC for each patient situation. Therefore, it is important for the oncologist to discuss CVC options, including risks and benefits, with the patient. It is important to explain to the patient that a central line may be inserted for one or more of the following reasons:

- Some chemotherapy drugs are not suitable to be administered into small veins in the hand or arm and must be administered in a larger vein for adequate dilution
- To allow some chemotherapy treatments, such as those administered by continuous infusion, to be administered at home and not require a lengthy hospital stay
- When extended chemotherapy treatments and frequent needle sticks to obtain blood samples are anticipated
- When a patient is felt to have poor venous access in the hands and arms not suitable for treatment infusions
- When a patient verbalizes or displays anxiety regarding needle sticks

When the oncologist and other practitioners determine that a CVC is required, it should be explained that a central line is a long narrow hollow tube made of soft plastic, which provides access to a large vein in the chest. The entrance location of the catheter is dependent on the type of central line, including tunneled, implanted, and PICC. Long-term CVCs can be used for medication administration, blood products, total parenteral nutrition, and blood drawing. Patients and caregivers of outpatients should be instructed about how to monitor for infection at the entrance-exit sites and to report other signs of infection or thrombosis such as fever or pain. The patient should be informed about his or her catheter, as follows:

Types of Catheters

Nontunneled catheters. When these catheters are used, they are most commonly placed into the subclavian vein (under the collar bone) or internal jugular vein in the neck. With proper care from a dedicated team, these catheters can facilitate the administration of fluids and chemotherapy as well as the drawing of blood samples, often for the entire duration of therapy. These will require sutures at the site where the catheter exits the skin. These catheters do not require that a patient go to the operating room or have general anesthesia, and they can be removed easily when no longer needed. In urgent situations for short-term use, these catheters can be placed into the large veins of the neck or groin but should be removed as quickly as possible because they carry a higher risk of complications.

Tunneled catheters. Tunneled catheters, sometimes referred to as Hickman catheters, are inserted by puncturing the vein below the collar bone or lower neck (the insertion site) and secured by threading

the line under the skin, exiting above the nipple on the chest wall (the exit site). The line may have a small Dacron cuff around it that imbeds into the tissue in the skin tunnel to prevent it from falling out. A small cut is made at both the insertion and exit sites, requiring one or two stitches in each. The stitches are removed in approximately 3 weeks when the cuff is secure, and the skin has healed. No needle sticks are needed with this type of catheter. Complications may include infection or bleeding at the entrance-exit site or in the subcutaneous tunnel, blood clots in or around the catheter, lung collapse during insertion, and catheter occlusion.

Implanted catheters. The implantable catheter or port consists of a catheter attached to a reservoir that is implanted into a surgically created pocket on the chest wall or upper arm. A needle is inserted through the skin to the septum of the port to access the reservoir. Advantages of this type of catheter are reduced risk of infection, less frequent flushing, and less interference with daily activities. Complications may include infection of the port site or catheter, blood clots in or around the catheter, lung collapse during insertion, and catheter occlusion.

Peripherally Inserted Central Catheters. The PICC line is inserted into the upper arm veins and threaded into the larger veins in the chest. This catheter is intended for patients requiring up to 12 months of IV therapy. An advantage of this type of catheter is the lack of needle sticks and placement at the bedside. Disadvantages include more frequent flushing and dressing changes. Complications may include infection at the exit site, blood clots in or around the catheter, and catheter occlusion. Placement of these types of catheters above the antecubital fossa diminishes the likelihood of thrombophlebitis.

Reliable venous access is critical for the patient with cancer to prevent delays in treatment. Effective communication among the oncologist, the individuals placing the venous access device, and most importantly the patient during the treatment-planning phase will promote improved patient outcomes. More patient information about CVCs in cancer treatment, including information about monitoring and caring for catheters at home, can be found at www.cancer.net, specifically www.cancer.net/patient/All+About+Cancer/Cancer.Net+Feature+Articles/Treatments%2C+Tests%2C+and+Procedures/Catheters+and+Ports+in+Cancer+Treatment.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Racial/ethnic minority patients with cancer suffer disproportionately from comorbidities, can experience substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poorer quality care than other Americans.[141-144] Many other patients lack access to care because they live at a distance from appropriate treatment facilities.

Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. In particular, the availability of adequate home care for catheter maintenance might vary widely among different patient populations and could influence the choice of CVC. The role of the oncologist/hematologist in guiding patient decisions should not be minimized. Furthermore, although in the overall scheme of a patient's care, the placement of a venous access device may seem minor, it can present difficulties that can dramatically affect a patient's ability to receive appropriate treatment.

ADDITIONAL RESOURCES

Data supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/cvc. Patient information is available at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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ART OF ONCOLOGY

Peers

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He is a perfect choice for the medical students' teaching session. The basic criteria are met: English-speaking, awake and alert, not being discharged or sent for a procedure, and most importantly, willing to undergo an hour-long history and physical. I make the necessary introductions and leave him and the students in each other's company, periodically checking in on their progress.

Later, after gathering with their classmates, the students are ready to share their findings. These early second–year oral presentations consistently prove challenging; the language and organization of even a normal physical examination is entirely foreign. Understanding this, I refrain from pointing out each misstep but cannot resist when they describe the patient as middle-aged. He is 31 years old.

I had heard his story making rounds on the oncology inpatient ward, yet it sounds different when it comes through medical students: first the seizure and then the diagnosis—glioblastoma multiforme—surgery, chemoradiotherapy, chemotherapy alone, scans, and "another" brain tumor. The students are surprised. I explain that they should not be.

"Did he know it would recur?" they ask.

"Yes."

"Why then does he also seem surprised?"

"I imagine knowing it and living it are two different things altogether."

Then there is more surgery and second-line chemotherapy.

"Will he be cured?"

"No."

They are again surprised; this time, they are sad.

It is awful to watch as the information sinks in. The students are so young and naive. None among this group is married or a parent; they have all been in school full-time without interruption since kindergarten. Having not had exposure yet to clinical medicine, the horrible diseases they are being introduced to in the classroom are abstract and academic. I wish I could preserve their innocence in its pure child-like state. Moments ago, they were asking for a detailed history of the patient's diet. Clearly pleased with his healthy lifestyle choices, they congratulated him on this and his positive attitude as these are surely important to his recovery, to his health, to his healing, and implicitly to his outcome. I want to tell him to have a cheeseburger and a chocolate milkshake for breakfast if he would like. I want to tell the students how little we control, as physicians and as human beings.

I thank the patient for his voluntary participation in medical education. He is what my grandmother would call an old soul. Aged by life experience compressed, he has accepted the unacceptable. He tells me of the trust fund he has established for his nieces and nephews. I promise to try to find the cute blonde from the pharmacy to bring his medications again.

In clinic, I tell the medical students I will see the next patient on my own. They are busy completing some documentation on the patients we just saw together, looking up diagnoses on Uptodate, and logging encounters to meet their educational requirements. Besides, as the next patient is being transferred to my care from a colleague, this is sure to be a delicate and difficult situation. What I already know of the case convinces me the patient would not want an entourage. Yet if I am honest with myself, it is I who prefer to be unaccompanied, who cannot possibly bring myself to explain this case. How could a 25-year-old be at the end of all standard-of-care options?

The young patient and I talk about phase I trials that she wants to pursue at other centers. I pretend not to notice that she is unfit even for those trials. We discuss tweaking her supportive care medications, controlling pain, using steroids, and scheduling intravenous fluid and electrolyte replacement. How optimistic I am that she will feel better if we can get her calcium down from its current 15 g/dL. And then the elephant in the room: code status and do not resuscitate orders, hospice, health care surrogate, who will care for her 19-month-old child. The medical students would learn from this discussion, I know, but it is more than I can bear.

It occurs to me that my patients and my students are, by age alone, peers. Their dress and prolific use of social media place them among those called Generation Y or Millennials. This nearly escaped me, given that, in all other aspects, the contrast between them is dramatic. The students are invigorating in their optimistic enthusiasm. They

are sure of themselves and the order of the world around them: hard work rewarded and life as planned. The patients are cautious, always aware that something—anything and even the most important thing—can go wrong without warning or reason. Their strength is humbling. Although robbed of time, they have a patience that awes me through the multitude of ways that illness and treatment make one wait. Their conversations possess a depth and perspective that the students' well-intentioned energetic chatter does not.

I become aware that I am treating the medical students like children, at once protecting, sheltering, and controlling what they are exposed to. I am paternalistically (maternalistically?) sure that I know what is in their best interest, what they can handle, and what is beyond them at their current stage. Yet the patients of the same age I treat like adults in the extreme, fully expecting them to make independent decisions about life and death, even preparation for their loved ones after they are gone.

Perhaps this is precisely the opposite of what they both need.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Ketamine and Cancer Pain: The Reports of My Death Have Been Greatly Exaggerated

TO THE EDITOR: We are writing in response to the article by Hardy et al, entitled, "Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain."[1] The authors are to be congratulated on successfully completing a placebo-controlled, randomized controlled trial in 185 patients receiving palliative care—no mean feat.

However, we question whether the authors' sweeping conclusion that "Ketamine does not have net clinical benefit when used as an adjunct to opioids and standard coanalgesics in cancer pain"[1(p3611)] is appropriate, when considering the way that many palliative medicine and pain medicine specialists use ketamine. Many of us have been using so-called burst ketamine for the last decade. Ketamine was used in this manner in two strictly controlled, open-label prospective audits,[2,3] which showed 29 of 43 and 22 of 44 positive responses, respectively. There is an obvious potential for observer bias and placebo responses in open-label trials; however, the differences between the results of Hardy et al and our own results may also be explained by differences in three factors: patient selection, the duration of ketamine use before it is deemed a treatment failure, and the management of psychomimetic adverse effects (AEs).

Ketamine is a so-called dirty drug, but its major postulated action in pain control is as an N-methyl-D-aspartate antagonist.[4,5] N-methyl-D-aspartate activation contributes to central sensitization, which occurs with ongoing nociceptive input from inflammation or injury and also seems to be one of the mechanisms that is associated with neuropathic pain states.[4,5] The clinical manifestations of central sensitization include ongoing and escalating pain, hyperalgesia, allodynia, and relative nonresponsiveness to opioids. It is indeed in patients who show these characteristics that we particularly advocate using ketamine, rather than in patients like those in the study by Hardy et al, who had "refractory chronic pain. . . typically for longer than 3 months" as per the protocol of Hardy et al.[1] Once established, central sensitization, together with the other neurophysiologic changes that are associated with pain chronicity, may not be reversible, and chronicity is recognized as a poor prognostic factor for achieving subsequent good pain control. Interestingly, there is increasing evidence that supports ketamine having an anti-inflammatory action at multiple levels.[4] Thus, its analgesic action may in part be a result of reducing the levels of pronociceptive cytokines such as interleukin-1β in the dorsal horn of the spinal cord. Additionally, pain mechanisms rather than pain etiology are increasingly being recognized as important in identifying the likely efficacy of any analgesic medication.[6] Hardy et al categorized the pains that they studied only as nociceptive or neuropathic. In our research, including our two audits, we found that somatic nociceptive pain achieves the best response—specifically, positive responses in 5 of 5 patients and 3 of 3 patients with mucositis pain, and 8 of 9 patients and 6 of 11 patients with bony metastases pain, respectively.[2,3] Thus, perhaps we and Hardy et al were studying dissimilar patient populations as defined by both chronicity and dominant pain mechanism(s)?

Hardy et al state that they used our dose-escalation protocol[3]; however, they deemed treatment to have failed if there was "no clinically relevant pain response"[1(p3614)] after 24 hours at the maximum dose of 500 mg over 24 hours, rather than after 3 days, as in our protocol. Additionally, we have learned from our experience over the last 10 years, and remembering that these patients have few other options, we now on occasion continue ketamine for up to 1 week before judging it to be ineffective. By ceasing ketamine after 24 hours if there was no meaningful response to ketamine at a dose of 500 mg administered over 24 hours, did the trial by Hardy et al miss a number of potential responders?

We concur with Hardy et al[1] on the potential for psychomimetic AEs (which seem to increase with increasing age and ketamine dose) and acknowledge that these would likely constitute an obstacle to long-term and/or outpatient treatment. The majority of AEs are National Cancer Institute[7] grade 1 or 2, although in our second audit we saw 11 National Cancer Institute grade 3 or 4 neurologic AEs in 44 patients[3] (and we now use prophylactic low-dose haloperidol or midazolam concurrently). However, no patient in either audit who had achieved a good response elected to cease ketamine early (and we specifically offered this option); that is, the patients seemed prepared to trade short-term AEs for long-term gain. Conversely, Hardy et al, because of the constraints imposed by their protocol, withdrew 22 of 93 patients because of toxicity. Again, how many of these patients were potential responders?

In summary, we contend that the conclusions from the article by Hardy et al[1] are valid only under the specific conditions of their protocol and do not necessarily apply to how we, and many others, use ketamine. We also suggest that the large body of contrary anecdotal evidence should not be dismissed without further investigation.

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Ketamine in the Management of Cancer Pain

To the Editor: I read the excellent article written by Hardy et al[1] in *Journal of Clinical Oncology*. Although the methodology and study design was of high scientific quality, there were several points that were not discussed in this interesting article.

As Hardy et al[1] pointed out, we have little evidence from controlled studies on ketamine use in patients with cancer with pain. However, when such a powerful drug is used, it is important to titrate the dose in a careful way. In this study, the presented schedule of dose increments was conducted during 5 days. The scheme was as follows: 100, 300, and 500 mg per day in a continuous subcutaneous infusion. Because the study duration was only 5 days, this scheme seemed to be an aggressive approach, especially when the daily dose was increased from 100 to 300 mg (by 300%). Because the careful titration of opioid analgesic is recommended, it seems that more-careful ketamine dose increments (eg, from 50 to 100, 150, 200, 250, and 300 mg) may be associated with less-adverse events. This effect might also be the case when the dose is increased from 300 to 500 mg.

Another interesting point in the study by Hardy et al[1] was that patients recruited at baseline experienced pain of moderate intensity (5.43 ± 1.3 and 5.21 ± 1.4 in the ketamine and placebo arms, respectively) according to the Brief Pain Inventory pain-on-average item. All patients had been treated at entry with high opioid doses (median oral morphine equivalents) of 300 mg (range, 160 to 480 mg) and 410 mg (range, 258 to 700 mg) in the ketamine and placebo arms, respectively. One of the entry criteria was that the average pain score was 3 or more on the Brief Pain Inventory. However, in clinical practice, a score of 3 or 4 may be acceptable for many patients, especially those suffering from neuropathic pain who usually experience severe pain (score > 6). High opioid doses might have contributed to the adverse effects observed.

From our experience, the indication on the concurrent use of opioids and ketamine could be severe neuropathic pain intensity (Numerical Rating Scale ≥ 7) that does not respond to opioids and adjuvant analgesics. The starting dose of ketamine should be low and titrated carefully to achieve satisfactory analgesia and acceptable adverse effects; then, the opioid dose may be reduced. Patients should be closely monitored at specialist in-patient units.[2,3] Ketamine may also be used for painful hygienic procedures or for changing dressings in patients after major burns.[4]

Mechanisms of ketamine analgesia include N-methyl-d-aspartate–receptor blockade, decrease of central sensitization, reduction of hyperalgesia, and reverse of opioid tolerance.[5] Results of controlled studies[1,6] have suggested a lack of efficacy and increased toxicity when ketamine and opioids were used concurrently. It seems that we need additional controlled studies with longer follow-up that could confirm or challenge these results and look for alternatives. One possibility is the use of methadone that combines the effects of the opioid agonist and N-methyl-d-aspartate–receptor antagonist. Uncontrolled reports demonstrated the efficacy and safety of small methadone doses added to other opioids, which may reduce risks associated with complex pharmacokinetics and appropriate dosing. Meanwhile, we should be grateful to Hardy et al[1] for conducting such a challenging study, and we should undertake additional controlled trials to find the best approach for patients with cancer with severe pain.

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Reply to K. Jackson et al and W. Leppert

We thank Jackson et al[1] and Leppert[2] for the opportunity to respond to their concerns regarding our article.[3]

Our main point of contention is the belief, on the part of Jackson et al,[1] that unblinded, nonrandomized, prospective audits can give a true indication of the efficacy or toxicity of a drug. Open-label studies do not meet the specific scientific definition of control. The gross underestimation and overestimation of effects in uncontrolled trials, especially studies that involve small numbers of participants, have been well documented.[4] This issue is particularly emphasized by the high placebo response rate (27%) demonstrated in our blinded, randomized controlled trial.

Regarding the issue of patient selection, we suggest that the median average pain scores, opioid equivalent doses at baseline, and selection criteria for resistant pain, despite previous and ongoing treatment with opioids and appropriate coanalgesia, defined the participants in our study as exactly those patients in whom Jackson et al[1] advocate the use of ketamine. The clinical manifestations of participants were consistent with those described as "central sensitization." Moreover, we suggest that the study population was reflective of the type of patient exposed to the drug in everyday clinical practice.

In a series of secondary analyses, we attempted to identify any subset of patient in whom ketamine might have benefit. We were unable to do so. Of interest, during our dissemination program, many clinicians have reported their preference for the use of drug in only patients with predominantly neuropathic pain rather than in patients with predominantly nociceptive pain as is the preference of Jackson et al.[1] This discrepancy emphasizes the lack of any international consensus on the use of this drug.

Another example of variation in practice is in the ketamine dose/toxicity issue. Other authors have suggested that a dose of 500 mg/24 h is excessive and, because of the potential toxicity of delivering this dose over a prolonged period, have chosen to start at a much lower dose.[5] None of these regimens are supported by formal toxicity assessments. We had ethical concerns in continuing the maximum dose for 3 days in the absence of any net clinical benefit. To clarify our study design, all participants with toxicity were given rescue midazolam and/or antipsychotics and offered dose reduction if indicated. Patients were only withdrawn if these measures were unacceptable to the patient or carer. Treating clinicians remained blind to the treatment allocation throughout the study.

We agree that the mechanism of action of ketamine as an N-methyl-D-aspartate antagonist and its role, if any, in central sensitization is postulated and not proven. Perhaps the next best step is to go back to the laboratory and undertake additional preclinical work in an attempt to determine the exact mechanism of any analgesic action of the drug in chronic as well as acute pain. Pain phenotypes have been described that may involve several independent neurobiologic mechanisms.[6] Targeted analgesia may be the way of the future.

We stand by our conclusion that subcutaneous ketamine when used in a dose-escalating regimen over 5 days confers no net clinical benefit at a population level for patients with advanced cancer. Furthermore, we were unable to identify any predictors of response in this cohort. The fact that these patients "have few other options" does not justify the use of a drug that is not only ineffective but also has significant toxicity. Although there is a large body of contrary anecdotal evidence, there is increasing evidence from randomized controlled trials that supports our claim.[7,8]

One of the problems inherent in the current use of ketamine in chronic pain is that there is no standard dose, schedule, or route of delivery. What has become apparent during our international dissemination process is that practice varies widely, ranging from low-dose oral ketamine given on an as-required basis to high-dose parenteral ketamine given as a continuous infusion over 5 days.[5] Many of these schedules are supported by anecdotal reports of dramatic relief from pain,[9] but none of these schedules have been tested formally for efficacy or toxicity in controlled clinical settings.

The regimen chosen for our study was discussed at length and was based on the largest series reported to date in the literature.[10] We agree entirely with Leppert[2] that it is important to "titrate the dose in a careful way." As illustrated in the study diagram (Fig 1), doses in this study were not fixed, and participants did not necessarily escalate to 500 mg over 5 days. Dose escalation and reduction were determined by a combination of both response and toxicity. Patients who showed a beneficial response at 24 hours to either a dose of 100 or 300 mg remained on that dose. Similarly, a dose reduction occurred in the case of failure to respond to rescue medications (antipsychotics and benzodiazepines) and unacceptable toxicity, which was consistent with the clinical assessment of the net clinical benefit.

The high attrition rate inherent in studies of patients with advanced disease is well recognized. The attrition rate of 20% over 5 days seen in our study was anticipated and would have increased significantly if we had used a used a slow titration regimen over a more-prolonged period as suggested by Leppert.[2] Patients with advanced cancer are unwell and often have rapidly progressive disease and an unstable condition. Our dose escalation-reduction regimen over 5 days took these conditions into consideration and rendered our study tenable.

With respect to the level of pain experienced by the participants, although our entry criteria allowed patients with an average pain score ≥ 3, it is clear from Figure 4 in our study that, at baseline, the majority of patients were suffering from at least moderate pain despite previous and ongoing treatment with opioids and coanalgesics. Moreover, the high dose of morphine equivalents recorded at baseline supported our premise that these patients had been taking opiods for some time.

The high incidence of adverse events recorded at baseline (Table 1) may well have been attributable to opioids. The randomization process ensured that the baseline toxicity was evenly distributed between arms. The adverse events reported in Table 3 were those that were scored as being worse than at baseline and were significantly greater in the ketamine arm. To our knowledge, our study is the first to have assessed the extent of ketamine toxicity in a formal prospective manner.

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Research on Chemotherapy-Induced Nausea: Back to the Past for an Unmet Need?

To the Editor: Control of chemotherapy-induced nausea, especially delayed nausea, remains an unmet need.[1] We read with interest the phase III trial by Roscoe et al,[2] and would like to comment on it and respond to the author's discussion of our own work.[3,4]

The article by Roscoe et al[2] is interesting in that it has been accepted without any data on control of vomiting, which is a primary determinant of the risk of delayed nausea (DN).[5,6] It would seem important to know if the control of nausea and vomiting on day 1 was the same in all three comparison groups. Also, one would like to know if the control of vomiting was the same in the delayed phase, for which only data on nausea are presented. We believe that all of the data in the appendix should be reported in the article because these data represent substantial information on the efficacy of the four study arms. In the article, the authors conclude that aprepitant was not more effective than prochlorperazine in controlling DN when both were combined with palonosetron and dexamethasone, but in the Appendix, they "moderate this lack of a statistically significant difference with what might be a clinically relevant benefit for patients receiving aprepitant" (online-only Appendix[2]). Furthermore, the vast majority of patients (95%) received an array of moderately emetogenic chemotherapy regimens, whereas only 5% of patients received highly emetogenic chemotherapy (HEC) containing cisplatin. The power for detecting clinically meaningful differences in average DN severity (primary end point) favoring palonosetron or aprepitant in the HEC setting is therefore weak. To overcome the issue of drugs that have different levels of emetogenicity, a post hoc analysis using data from only patients with breast cancer (54% of the study cohort) receiving doxorubicin-based chemotherapy was performed. Although this unplanned analysis confirmed the overall findings, the case-mix remains a major issue in the interpretation of results. Overall, these questions prevent us from being confident in concluding that palonosetron and granisetron on day 1 carry similar efficacy against DN when prochlorperazine is given on days 2 and 3. The same is true for the observation that when palonosetron was used, aprepitant provided no significant benefit compared with prochlorperazine in preventing DN in patients undergoing HEC or moderately emetogenic chemotherapy.

The absolute difference in DN rates among patients receiving prochlorperazine compared with those receiving a first-generation serotonin antagonist on days 2 and 3 was only 8 percentage points (DN rate from 71% to 79%) in the previous study.[7] In the present study,[2] there was no significant difference in DN rates among patients receiving prochlorperazine compared with those receiving prochlorperazine plus dexamethasone (61% *v* 52%) on days 2 and 3. Likewise, no significant difference in DN rates was observed between the treatment groups receiving either aprepitant plus dexamethasone or prochlorperazine plus dexamethasone (47% *v* 52%) on days 2 and 3. Third, in the group receiving aprepitant, patients experienced less delayed vomiting and also had significantly less DN if vomiting did occur. These data indicate that prochlorperazine may play a specific role in DN when acute emesis is well controlled.

The authors state that more effective regimens against DN should include prolonged dexamethasone, but the benefit of delayed dexamethasone dosing when combined with palonosetron remains an open question. A meta-analysis of individual patient data that we conducted in patients with breast cancer receiving a uniform emetogenic stimulus caused by the combination of an anthracycline plus cyclophosphamide showed that there was no difference in number of nausea-free patients between the treatment groups receiving palonosetron plus 1-day or 3-day dexamethasone during the delayed and overall phases.[8] Also, in the high-risk subgroup of patients age 50 years or younger, there was no difference in the number of nausea-free patients between treatment groups during the 5 days after chemotherapy.

The findings by Roscoe et al[2] may be misleading for readers who are not experts in the chemotherapy-induced nausea and vomiting (CINV) field because they do not really support any departure from

the evidence-based antiemetic guidelines.[9,10] We need to build on the state-of-the-art knowledge about CINV to improve the management of our patients. Palonosetron and aprepitant offer significant advantages compared with older agents, and this is reflected in recently updated international guidelines.[9,10] If the ultimate goal in CINV research is no nausea and vomiting in patients undergoing chemotherapy, a more appropriate and reliable efficacy end point for future trials would be complete protection (defined as no vomiting, no rescue antiemetics, and no nausea) during the 5 days after chemotherapy.

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Antipsychotics-Containing Regimen As an Alternative to Standard Antiemetics for Delayed Nausea Induced by Highly Emetogenic Chemotherapy

To the Editor: Roscoe et al[1] recently presented data from a double-blind randomized clinical trial to determine the efficacy of the addition of dexamethasone on days 2 and 3, a second-generation 5-hydroxytryptamine receptor antagonist (5-HT RA; palonosetron), and a neurokinin-1-receptor antagonist (aprepitant) for delayed nausea. This study failed to show the benefit of palonosetron and aprepitant compared with a standard regimen that included prochlorperazine. The authors commented that most randomized trials reporting the efficacy of aprepitant did not use effective alternative medication, such as prochlorperazine, for delayed nausea. Among the 5-HT RAs, the effects of palonosetron and granisetron for controlling delayed nausea are similar, provided that prochlorperazine is used.[1] Prochlorperazine, an antipsychotic, acts on dopaminergic receptors at the chemoreceptor trigger zone, possibly at other CNS centers, and peripherally. Prochlorperazine may be most frequently used for nausea and vomiting.[2]

Another antipsychotic, olanzapine (OLN), blocks receptors of multiple neurotransmitters: dopamine receptors (as with prochlorperazine), serotonin receptors, alpha-1 adrenergic receptors, muscarinic receptors, and H_1 receptors.[3] OLN was shown in a randomized phase III trial to be as effective as aprepitant for antiemesis during highly emetogenic chemotherapy (HEC).[4] We retrospectively reviewed consecutive patients with early breast cancer who underwent adjuvant or neoadjuvant chemotherapy with HEC and were refractory (mostly because of grade 3 nausea or vomiting) to the standard antiemetic regimen as determined after the first cycle of chemotherapy at our hospital from January 2009 to December 2010 (before aprepitant became available in our institution). For the second cycle, the patients received 2.5 to 10 mg OLN per day, from days 1 to 3, in addition to the standard antiemetic regimen (5-HT RAs and dexamethasone 20 mg intravenously on day 1, and 4 mg dexamethasone orally or intravenously per day on days 2 and 3). Of the 12 women who received HEC and OLN, grade 3 nausea and vomiting was reduced from 42% to 8% and from 67% to 0%, respectively. Surprisingly, 42% of patients required no breakthrough antiemetic treatment despite poor control during the preceding cycle. No grade 3 or 4 adverse events

thought to be related to OLN were noted, but 67% and 33% of patients complained of grade 1 to 2 drowsiness and dizziness, respectively. These events prompted a reduction in dose or duration of OLN; nevertheless, efficacy was retained.

In Japan, the per-cycle cost of OLN used in the trial was approximately ¥2,000 (equivalent to approximately $22), and that of aprepitant was about ¥15,000 ($167). The cost of prochlorperazine per cycle in the study by Roscoe et al[1] was about ¥120 ($1.3). In line with the cost of standard chemotherapy—for example, the cost of doxorubicin and cyclophosphamide per cycle is about ¥20,000 ($222)—the medication for supportive care is as expensive as the antineoplastics. Therefore, antipsychotics such as prochlorperazine and OLN are not only effective for prevention of chemotherapy- induced nausea and vomiting, but also highly cost-effective.

Reconsideration of the antiemetics guideline may be important, especially when pharmacoeconomics for developing countries are concerned. With the use of inexpensive antipsychotics in addition to dexamethasone and a first-generation 5-HT RA, palonosetron and a neurokinin-1 receptor antagonist add little other than expense. Large randomized clinical trials with a placebo are difficult to conduct without financial support from pharmaceutical companies. Therefore, clinical trials that are designed to study noninferiority of cost-saving strategies are rarely conducted. Until the data clearly indicate that the next-generation 5-HT RAs and/or neurokinin-1-receptor antagonists are superior to the more cost-effective regimen, which uses dexamethasone, a first-generation 5-HT RA, and antipsychotics, this regimen may serve as an alternative, especially for a medically underserved population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Reply to L. Celio et al and H. Ishiguro et al

We are pleased to have the opportunity to address the concerns with our article[1] that were raised by Celio and Aapro.[2] First, we agree with them that the article would have been strengthened by inclusion of the data on vomiting in the published article rather than in the online appendix. Journal space constraints combined with the fact that delayed nausea (DN), not vomiting, was our primary outcome dictated this choice. The data we provided online directly address the concerns of Celio and Aapro regarding control of vomiting and nausea on day 1. In brief, 39% of subjects reported acute nausea (any level) on day 1, and there were no significant differences between groups with respect to average acute nausea ($P = .827$), maximum acute nausea ($P = .834$), nor incidence of acute nausea ($P = .819$). Ten percent of subjects reported vomiting on day 1. Using logistic regression that controlled for chemotherapy regimen and Community Clinical Oncology Program site, there were no significant differences between treatment groups ($P = .501$). Sixteen percent of the patients vomited at least once during days 2 or 3 (group 1, 18%; group 2, 24%; group 3, 8%; group 4, 14%). We conducted comparisons between groups 1 and 2, groups 1 and 4, and groups 3 and 4 on incidence of delayed vomiting (DV) using logistic regression. The P values for these three comparisons were .216, .218, and .031, respectively, with none meeting the Bonferroni corrected criterion for statistical significance of .017.

With respect to the concern over the case-mix of moderately emetogenic chemotherapy and highly emetogenic chemotherapy, we note that combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic in the 2011 update of the American Society of Clinical Oncology antiemetic guidelines.[3] Under this reclassification, 59% of our patients received highly emetogenic chemotherapy, including all in the subgroup analyses of patients with breast cancer referred to by Celio and Aapro.[2]

Celio and Aapro[2] are correct in stating that there was no significant difference in DN rates among patients receiving prochlorperazine compared with those receiving prochlorperazine plus

dexamethasone (61% *v* 52%) on days 2 and 3. Although true, we are not sure of its relevance when the more detailed measure of average nausea, which was our primary outcome, and peak nausea were each significantly improved by the addition of dexamethasone on days 2 and 3. Rather than using a simple dichotomous measure of yes or no to assess nausea rates, we used average nausea on the basis of 11 assessment points, each on a 7-point scale. The peak nausea variable in our analyses was the highest nausea reported at any of these 11 reporting points.

Celio and Aapro[2] raise an important point regarding aprepitant for control of vomiting. In our discussion of vomiting in the online-only Appendix,[1] we noted that although aprepitant was not more effective than prochlorperazine in controlling DN when both were combined with palonosetron and dexamethasone, this lack of a statistically significant difference could be moderated with what might be a clinically relevant benefit for patients receiving aprepitant. That is, patients receiving aprepitant had a nearly statistically significant lower incidence of DV than patients receiving prochlorperazine (8% *v* 14%), and also had significantly less DN if DV did occur. Concerning the assessment of Celio and Aapro that our "data indicate that prochlorperazine may play a specific role in DN when acute emesis is well controlled," we concur, provided that the word "delayed" is substituted for the word "acute." However, we think a better way to conceptualize our findings is to say that aprepitant may be more helpful than prochlorperazine in approximately 14% of patients, either by providing more effective control of DV or by helping to control nausea when DV does occur.

Given that we found no benefit of palonosetron compared with granisetron in any of our analyses and, for 86% of patients, there was no benefit of aprepitant compared with prochlorperazine, we suggest that the widespread use of palonosetron be reconsidered, and a more targeted approach be used for aprepitant.

We are also pleased with the positive comments on our article by Ishiguro et al.[4] They raise important issues not addressed in our article[1] concerning the substantially greater costs of the newer antiemetics compared with the older generic ones, and concerning the financial support and design of large antiemetic trials. Their points are well taken.

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Dexrazoxane Prevention of Anthracycline Cardiomyopathy

To the Editor: The review article by Lenihan and Cardinale[1] does not mention that dexrazoxane has had US Food and Drug Administration approval since 2002, as well as American Society of Clinical Oncology agreement that it protects against the cardiotoxic effect of doxorubicin without reducing the antitumor effect of this drug.[2-4]

As mentioned in the review article,[1] for carvedilol and enalapril to be accepted, it would need to be shown in a comparative trial that in all respects, these agents are superior or at least equal to dexrazoxane. Any review on the reduction of anthracycline cardiotoxicity that fails to mention the distinguished work on the activity of dexrazoxane by Herman and Ferrans,[5] Swain and Vici,[2,6] Lipshultz et al,[7] and Ewer[2] gives not only an incomplete overview, but also a misleading one.

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Reply to R. Steiner et al

We graciously acknowledge the expert opinion of Steiner and Hellmann[1] regarding statements about cardioprotection during anthracycline-based chemotherapy. In our review,[2] we did acknowledge that dexrazoxane was a therapeutic option for cardioprotection and referenced a major review on the use of cardioprotectants.[3] Because our review was focused on late cardiac effects of cancer treatment, we were unable to carefully detail all of the relevant studies that potentially addressed early or acute cardiotoxicity from anthracyclines, although we do agree conceptually with Steiner and Hellmann that prevention is the best strategy.

Furthermore, we recognize that American Society of Clinical Oncology 2008 Clinical Practice Guideline[4] suggests the use of dexrazoxane in specific adult patients (patients with breast cancer who have received > 300 mg/m^2 of anthracyclines) on the basis of work from Swain[5,6] and others.[7,8] Additionally, Lipshultz[9] has published authoritative reports on the effective use of dexrazoxane in childhood leukemia.

However, it is certainly our observation and that of others[10] that dexrazoxane has a significantly limited use in adult patients who receive anthracyclines.[11] This may be in part a result of attenuation of the cancer efficacy of anthracyclines or the potential concern of late effects, such as secondary leukemia.[12] In fact, the use of dexrazoxane in children is not recommended in Europe.[13] Conversely, angiotensin-converting enzyme inhibitors and carvedilol are ubiquitously used clinically, and their long-term safety is well established. These classic cardiac medications are known to be cardioprotective with chemotherapy,[14,15] especially anthracyclines, and the ease of administering this medication(s) during chemotherapy is understood. We agree that no study has directly compared dexrazoxane cardioprotection with angiotensin-converting enzyme inhibitors or carvedilol in the context of anthracycline chemotherapy, and it seems highly unlikely that such a study will be performed.

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