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ORIGINAL REPORT

Rituximab Purging and/or Maintenance in Patients Undergoing Autologous Transplantation for Relapsed Follicular Lymphoma: A Prospective Randomized Trial From the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

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Processed as a Rapid Communication manuscript. See accompanying editorial on page 1617; listen to the podcast by Dr Ghielmini at www.jco.org/podcasts

A B S T R A C T

Purpose

The objective of this randomized trial was to assess the efficacy and safety of rituximab as in vivo purging before transplantation and as maintenance treatment immediately after high-dose chemotherapy and autologous stem-cell transplantation (HDC-ASCT) in patients with relapsed follicular lymphoma (FL).

Patients and Methods

Patients with relapsed FL who achieved either complete or very good partial remission with salvage chemotherapy were randomly assigned using a factorial design to rituximab purging (P+; 375 mg/m^2 once per week for 4 weeks) or observation (NP) before HDC-ASCT and to maintenance rituximab (M+; 375 mg/m^2 once every 2 months for four infusions) or observation (NM).

Results

From October 1999 to April 2006, 280 patients were enrolled. The median age was 51 years (range, 26 to 70 years), and baseline characteristics were well balanced between groups. On average, patients were 44 months (range, 3 to 464 months) from diagnosis, with 79% having received two lines and 15% three lines of prior therapy. Median follow-up was 8.3 years. In contrast to purging, 10-year progression-free survival (PFS) was 48% for P+ and 42% for NP groups (hazard ratio [HR], 0.80; 95% CI, 0.58 to 1.11; $P = .18$); maintenance had a significant effect on PFS (10-year PFS, 54% for M+ and 37% for NM; HR, 0.66; 95% CI, 0.47 to 0.91; $P = .012$). Overall survival (OS) was not improved by either rituximab purging or maintenance.

Conclusion

Rituximab maintenance after HDC-ASCT is safe and significantly prolongs PFS but not OS in patients undergoing transplantation for relapsed FL. Pretransplantation rituximab in vivo purging, even in rituximab-naive patients, failed to improve PFS or OS.

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INTRODUCTION

Chemotherapy results in high first remission rates for the majority of patients with follicular lymphoma (FL), but after relapse, both the response rate and duration of remission to subsequent salvage treatment steadily decreases.[1-4] High-dose chemotherapy and autologous stem-cell transplantation (HDC-ASCT) have been used to improve outcome in patients with FL recurrence. Single-center studies and registry analyses have revealed 10-year progression-free survival (PFS) rates between 30% and 50%.[5-7] In the only prospective randomized trial, significant improvements in 2-year PFS and overall survival (OS) were observed, with no benefit from in vitro purging. A PFS of 63% was observed in patients with relapsed FL after HDC-ASCT, compared with a PFS of 33% ($P = .004$) in patients randomly assigned to chemotherapy alone.[8]

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The addition of rituximab to conventional chemotherapy in FL has significantly improved outcome during the last decade.[9] However, there is no plateau on the PFS curves, with patients continuing to relapse.[10-12] A retrospective analysis of patients who relapsed after rituximab-containing first-line therapy showed that patients re-treated with rituximab at relapse had a significant 3-year PFS advantage over those not receiving rituximab; this benefit was also demonstrated in patients undergoing transplantation.[13]

Although the role of maintenance rituximab has been established in relapsed FL after induction with rituximab-containing chemotherapy, chemotherapy alone, or rituximab monotherapy, the benefit and safety of maintenance rituximab after HDC-ASCT are unknown.[9,14,15] Although preliminary data from phase II studies have suggested that rituximab maintenance therapy after HDC-ASCT may be associated with prolonged clinical and molecular remissions in patients with FL,[16-18] there has been no evidence from comparative studies that rituximab maintenance is beneficial after HDC-ASCT.

Thus, the best second-line treatment in FL and the roles of HDC-ASCT and maintenance rituximab after ASCT remain of major interest. To our knowledge, this is the first randomized prospective study investigating the efficacy and safety of rituximab when administered as an in vivo purging agent before the collection of hematopoietic stem-cell product and/or as post-transplantation maintenance to consolidate remission.

PATIENTS AND METHODS

Patient Eligibility

Eighty-seven centers in 13 countries participated in the EBMT LYM1 (European Group for Blood and Marrow Transplantation Lymphoma 1) trial. This was a prospective open-label randomized phase III study in patients with rituximab-naive chemosensitive relapsed CD20+ FL in complete (CR) or very good partial remission (VGPR; defined as $>$ 50% reduction in all lesions with no residual mass $>$ 5 cm and $<$ 25% bone marrow [BM] involvement) who had received one to three prior chemotherapy regimens. Patients with evidence of histologic transformation and those who had previously received a transplantation or extensive prior radiotherapy were excluded. Histologic material was peer reviewed by expert lymphoma pathologists. Salvage chemotherapy for treatment of progression or relapse was not part of the protocol. Data concerning date of diagnosis, date and site of progression or relapse, presence of histologic transformation, and second-line treatment type were reported by local investigators. The protocol was approved by local or national ethics committees and national regulatory agencies according to national laws. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines, with written informed consent obtained according to local rules.

Study Design and Treatment

Four hundred eighty patients with chemosensitive FL were to be randomly assigned to rituximab purging (P+; 375 mg/m^2 intravenously [IV] once per week for 4 weeks) versus no purging (NP) and to maintenance (M+; 375 mg/m^2 IV once every 2 months for four infusions) versus no maintenance (NM) using a minimization procedure that included stratification by disease status at random assignment: CR versus VGPR and first versus second or subsequent response (Figs 1 and 2).

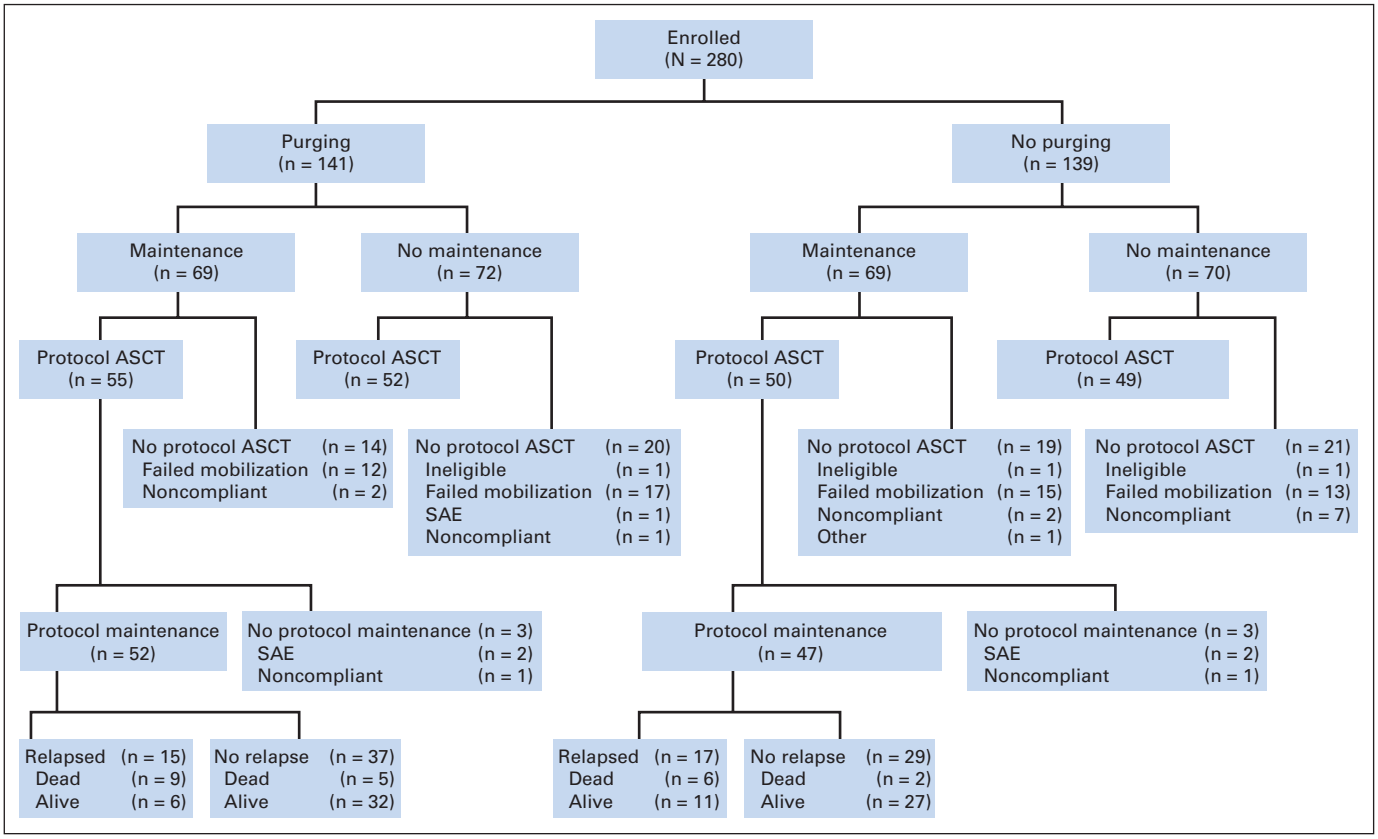

Fig 1. CONSORT diagram. ASCT, autologous stem-cell transplantation; SAE, serious adverse event.

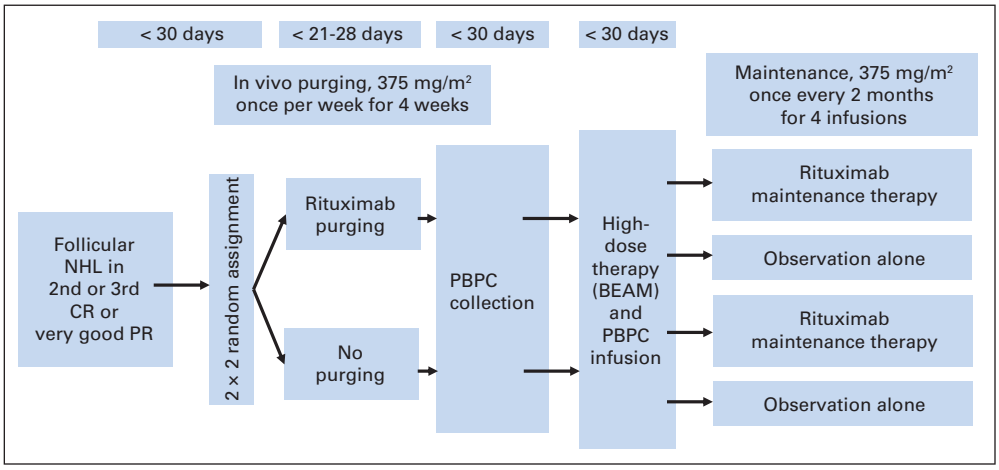

Fig 2. Trial design. B-cell depletion by rituximab and/or no treatment was established at random assignment in a 2 × 2 design. BEAM, carmustine, etoposide, cytarabine, and melphalan; CR, complete remission; NHL, non-Hodgkin lymphoma; PBPC, peripheral blood progenitor cell; PR, partial remission.

The trial was stopped early because of slow recruitment. In agreement with the data monitoring committee, the follow-up of existing patients was continued until the number of events necessary to achieve comparable significance and power levels as originally intended (described under Statistical Analysis) had been reached. Patients were observed until the end of 2011, with a median follow-up of 8.3 years. There were no differences in median follow-up across the four treatment groups. The intervals from induction to random assignment were defined as 30 days and from random assignment to transplantation as 51 to 58 days (Fig 2). Patients allocated to purging received 375 mg/m^2 rituximab within 4 weeks of staging after induction chemotherapy. Peripheral blood progenitor cells (PBPCs) were mobilized with cyclophosphamide 1.5 g/m^2 and granulocyte colony-stimulating factor (filgrastim) 10 μg/kg as a daily subcutaneous injection from day 2 to PBPC collection. A minimum yield of 2.0 × 10^6/kg CD34+ cells was required. All patients received BEAM (carmustine, etoposide, cytarabine, and melphalan) high-dose chemotherapy, and first infusion of rituximab maintenance was planned to start 30 days after PBPC infusion. During the first year of rituximab maintenance/observation, patients were seen at least every 3 months, then every 6 months for 2 years, and then annually, with tumor assessments required at each visit. Computed tomography (CT) and BM examinations were performed only on indication. However, in occurrences of progression or relapse, detailed information on the date and site of progression/relapse had to be provided by the investigator, which required a repetition of the original radiologic assessments performed at study entry.

Statistical Analysis

Patients were randomly assigned using a 2 × 2 factorial design to compare rituximab P+ versus NP and rituximab M+ versus NM, allowing both questions to be answered for the same number of patients. Random assignment was stratified by CR versus VGPR and number of remissions.

The primary end point for comparisons within each factor (P+ and M+) was PFS. The trial was designed to have an 80% chance of detecting a 15% difference in outcome at 4 years, with a two-sided level of significance of .05.

All primary analyses were conducted on intention to treat. PFS was defined as the interval between date of random assignment and date of first relapse, progression, or death; no competing risks were considered significant in this setting. Standard parametric and nonparametric tests for comparing populations were used throughout to test for balance between groups. Where a large number of tests were necessary, multiple testing CIs were built. Log-rank test, Kaplan-Meier plots, and Cox regression were used for survival analysis. Statistical analysis was performed using STATA software (STATA, College Station, TX). All *P* values provided are two sided and were deemed significant at the .05 level.

RESULTS

From Oct 1999 to April 2006, 280 rituximab-naive patients with relapsed chemosensitive FL were randomly assigned: 141 patients to P+ and 139 to NP, and 138 patients to M+ and 142 to NM. There were no significant differences in patient characteristics between the two arms (Table 1). Various chemotherapy regimens had been administered to reinduce remission (predominantly CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] –like or fludarabine- or platinum-based regimens). Response after reinduction chemotherapy was CR in 84 patients (30%) and VGPR in 196 (70%). The median time intervals were 31 days (range, −25 to 1,194) from salvage chemotherapy to random assignment and 55 days (range, 14 to 195) for NP and 83 days (range, 50 to 207) for P+ patients from random assignment to PBPC infusion.

A total of 80 patients (29%) were withdrawn from study (Fig 1); withdrawals did not differ between treatment groups. Only six patients (2%) were withdrawn after transplantation; 57 patients (20%) did not mobilize; three patients were not eligible (most received rituximab with induction chemotherapy); and 14 patients were noncompliant; five withdrew as a result of a severe adverse event and one withdrew for other reasons.

There was a significant difference in the number of CD34+ cells infused between the P+ (3.75 × 10^6 CD34+ cells/kg) and NP (5 × 10^6 CD34+ cells/kg) groups ($P = .04$). This difference, however, did not affect outcome when tested in the multivariate model. No differences between groups were found in the intervals from diagnosis to random assignment or in the intervals from diagnosis to transplantation. ASCT was performed in 206 patients (74%). After a median of 31 days (range, 14 to 389) from PBPC infusion, 99 patients commenced maintenance rituximab, with 86 completing the four treatments.

Death and Progression

One hundred twenty-nine patients (46%) progressed, and 75 (27%) died. Of the patients who progressed, four did so before treatment, seven during protocol treatment (four during maintenance rituximab), and 41 off protocol; the remaining 77 patients progressed during follow-up.

Table 1. Patient Characteristics at Baseline According to Random Assignment (N = 280)

Characteristic	No Purging or Maintenance (n = 70)	Purging; No Maintenance (n = 72)	Maintenance; No Purging (n = 69)	Purging and Maintenance (n = 69)	Total (N = 280)
Follicular histology, %	100	100	100	99	99.6
Male sex, %	54.3	55.6	53.6	44.9	52
Age, years					
Mean	51	50	53	52	51.6
Range	26-68	26-70	33-68	31-70	26-70
ECOG PS > 0, %	22.4	18.6	24.6	22.1	22.4
Bulky disease, %	20.3	25.4	22.1	17.9	21.8
BM involvement, %	37.3	29.6	30.4	35.2	33.1
Prior lines of chemotherapy, %					
One	8.6	5.6	1.4	7.2	5.7
Two	81.4	79.2	82.6	73.9	79.3
Three	10.0	15.3	15.9	18.8	15.0
FLIPI, %					
Low	28.6	33.9	34.5	37.5	33.6
Intermediate	36.7	28.6	32.8	37.5	33.9
High	34.7	37.5	32.8	25.0	32.5
Response to induction, %					
CR	30.0	30.6	31.9	27.5	30.0
VGPR (> 90%)	70.0	69.4	68.1	72.5	70.0

Abbreviations: BM, bone marrow; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognosis Index; VGPR, very good partial remission.

Transplantation-related mortality, defined as nonrelapsed death within 100 days of transplantation, was 0.4% corresponding to one death of cardiac toxicity. Twelve other deaths occurred in patients after 100 days who were in remission and on protocol. Causes included thrombotic thrombocytopenic purpura, cerebral infarction, cardiac arrest, radiation-induced sarcoma, and other toxicities, including four associated with a secondary malignancy or its treatment. Of the remaining 62 deaths, 55 occurred after progression or complications associated with treatment after relapse. Of the seven patients who died without progression but after abandoning the protocol, one patient had no reported cause of death, two had a secondary malignancy, and four, who were withdrawn from protocol because of mobilization failure or withdrawal of consent, died as a result of complications of nonprotocol treatment. Deaths were evenly distributed across treatment groups.

Overall, secondary malignancies were reported in 11 patients who died at intervals ranging from 9 months to 8 years after random assignment, with no significant differences in distribution across groups or number of CD34 cells infused. Six patients (two on protocol) developed acute myelogenous leukemia, and one patient (on protocol) developed myelodysplastic syndrome. An additional patient developed breast cancer but is alive in remission 10 years after random assignment.

PFS

As per random assignment, in vivo purging with rituximab 375 mg/m^2 once per week for four infusions before PBPC collection had no effect on PFS (Fig 3A). At 10 years, PFS was 48.6% (95% CI, 39.6% to 56.9%) for P+ patients and 42.0% (95% CI, 33.5% to 50.4%) for NP patients (P+ *v* NP: hazard ratio [HR], 0.80; 95% CI, 0.58 to 1.11; $P = .18$). Maintenance rituximab had a significant effect (Fig 3B). At 10 years, PFS was 54% (95% CI, 45.0% to 62.2%) for M+ compared

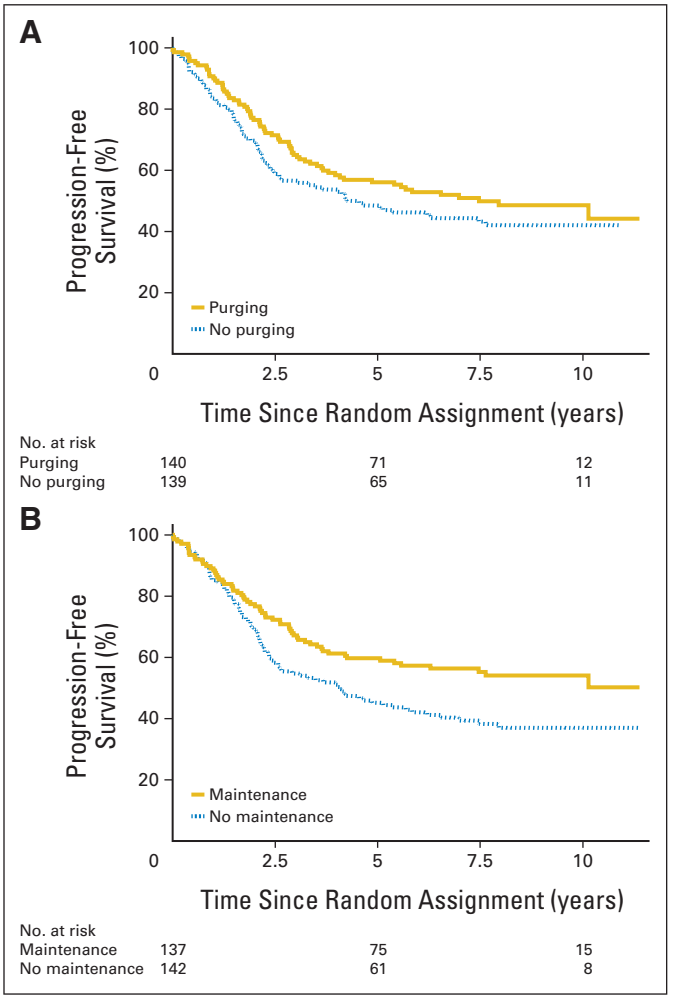

Fig 3. Effect on progression-free survival of (A) rituximab purging and (B) rituximab maintenance by intention to treat from date of random assignment.

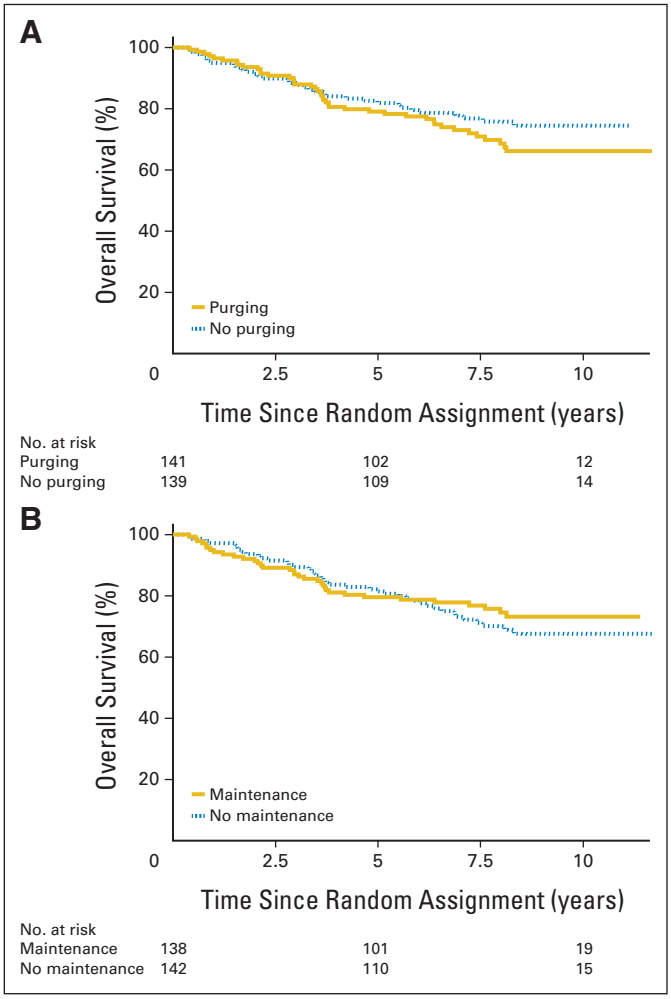

Fig 4. Effect on overall survival of (A) rituximab purging and (B) rituximab maintenance by intention to treat from date of random assignment.

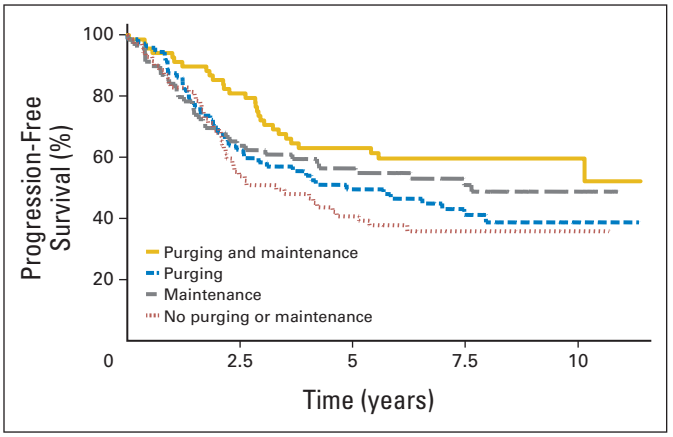

Fig 5. Progression-free survival by treatment arm.

with 37.0% (95% CI, 28.6% to 45.3%) for NM patients (HR, 0.66; 95% CI, 0.47 to 0.91; $P = .012$).

OS

Neither purging nor maintenance had an effect on OS. At 10 years, OS was 66.1% (95% CI, 56.7% to 74.0%) for P+ and 74.5% (95% CI, 65.8% to 81.3%) for NP patients (Fig 4A). Ten-year OS was 73.1% (95% CI, 64.2% to 80.2%) for M+ and 67.8% (95% CI, 58.3% to 75.2%) for NM patients (P = NS; Fig 4B).

PFS and OS According to Treatment Group

There was a trend toward improvement in PFS at 10 years in patients who received rituximab: no rituximab, 35.8% (95% CI, 24.6% to 47.2%); P+, 38.7% (95% CI, 26.8% to 50.5%); M+, 48.8% (95% CI, 36.0% to 60.4%); and P + M, 52.1% (95% CI, 34.0% to 67.5%; test for trend: HR, 0.98; $P = .028$; Fig 5). Median PFS was 2.64 years in patients who received no rituximab, 4.18 years in the P+ group, and 7.46 years in the M+ group; it was not reached in the P + M group. Most transplantation literature reports outcomes from date of transplantation. Median PFS from date of transplantation was 3.3 years for no rituximab, 5.5 years for P+, > 10.5 years for M+, and 9.5 years for P + M groups. There was no difference in OS at 10 years by treatment group.

Multivariate Analysis of OS and PFS

Cox regression models were run for OS and PFS, analyzing age, sex, performance status, remission status at time of transplantation, time from diagnosis to transplantation, number of lines of prior therapy, type of initial therapy and chemotherapy at progression, chemosensitivity, CD34 cell dose, relapse < 12 months, Follicular Lymphoma International Prognostic Index score (0 to 1 *v* 2 or ≥ 3), and total rituximab dose. Only maintenance rituximab affected PFS (HR, 0.66; 95% CI, 0.47 to 0.91).

Safety

Toxicity was measured on a large number of parameters, but only fever, diarrhea, nausea, vomiting, abdominal pain, and infection appeared with any frequency. Early or late toxicities did not differ significantly across the treatment groups. The time to engraftment was rapid, with median time to recovery of neutrophils $> 0.5 \times 10^9$/L of 14.3 days (range, 10 to 115 days; n = 168) and platelets $> 50 \times 10^9$/L of 25.1 days (range, 9 to 190 days; n = 158). There were no significant differences between the treatment groups and a single patient failed to engraft. There were no infection-related deaths in the first 100 days.

In the M+ group, there was a systematic, although nonsignificant, lowering of neutrophils compared with the NM group during the first year after random assignment (Appendix Fig A1, online only). A reduction to neutrophils $< 500\ 0.5 \times 10^9$/L was seen in two patients within 30 days of transplantation with no sequelae. Three infection-related deaths occurred at 10 months and at 4.2 and 4.7 years. Four first-infusion rituximab-related serious adverse events were reported, which resulted in two patients being withdrawn from study.

DISCUSSION

The role of rituximab maintenance after conventional (immuno) chemotherapy in patients with FL has been established in the first-line and salvage settings.[9,11] To our knowledge, our study shows for the first time that in patients with relapsed chemosensitive FL who were treated with HDC-ASCT, four infusions of rituximab maintenance over 8 months was associated with statistically significant longer PFS.

There was no demonstrable benefit in OS. This is in line with preliminary data reported by Hicks et al,[18] who showed that this approach might offer durable molecular remissions and prolonged PFS in patients with FL.

This trial showed no benefit with rituximab in vivo purging after induction chemotherapy, but the analysis was underpowered, so patients will continue to be observed. Neither ex vivo purging[8] nor assessment of molecular remissions by Hicks et al[18] showed benefit with rituximab as a single agent administered before HDC-ASCT. However, rituximab administered as a single agent is less effective than rituximab administered with chemotherapy.[1,10-12,19,20] The combination of rituximab and chemotherapy as first-line treatment has been investigated in five randomized phase III trials to date. All concluded in favor of the rituximab-containing regimen and established that rituximab at first induction improves response duration.[1,10-12,19] Two randomized studies demonstrated in rituximab-naive patients that adding rituximab to salvage therapy at first relapse (followed by rituximab maintenance) increased response rates and improved disease-free survival.[9,14,20] Rituximab administered in this way provides both effective in vivo purging and improved remission. Thus, although we could not show a beneficial effect of pretransplantation rituximab directly, one may speculate given the positive trend test in favor of rituximab purging and maintenance across the four groups that either the total dose of rituximab or the longer administration of rituximab favorably influenced PFS, as observed in the nontransplantation setting.[21]

Our data underline the favorable impact of HDC-ASCT in disease control, as reported in the CUP (Chemotherapy Versus Unpurged Versus Purged)[8] and Le Gouill et al[13] studies, which both showed a significant advantage to receiving HDC-ASCT versus chemotherapy alone in both rituximab-naive and rituximab-pretreated patients. In our study, the median PFS for patients receiving rituximab purging and maintenance (not reached) or maintenance alone (7.46 years) far exceeded that observed in patients with relapsed/refractory FL receiving maintenance after rituximab plus CHOP (median PFS, 3.7 years) reinduction chemotherapy.[12]

As in other studies, FL relapse after HDC-ASCT followed a biphasic pattern with continuing relapse during the first 6 years and only a few events thereafter,[22] resulting in a plateau on the relapse curve of 50% at 7.5 years. This observation is in line with previous reports on extended follow-up of FL after HDC-ASCT[5] and indicates that HDC-ASCT might be capable of providing sustained control or even eradication of FL for a subset of patients.[5,6,13,22]

Because this study enrolled patients who were rituximab naive, it remains unclear whether HDC-ASCT will be beneficial for patients who relapse after rituximab-containing first- or second-line regimens. A recent retrospective analysis of patients with relapsed FL suggested not only that patients undergoing transplantation have a longer remission than those who do not but also that this benefit may extend to patients who received rituximab as first-line treatment and at progression.[13] Maintenance rituximab did not significantly improve OS in our study, but it is likely that rituximab was administered to all patients in the NM arm who progressed. The impressive OS at 10 years suggests that salvage chemotherapy after HDC-ASCT and maintenance rituximab are effective in the majority of patients.

In contrast to the EBMT registry study, we were unable to identify patient or disease characteristics that would identify a poor outcome.[5,23] In the 175 patients who relapsed after the FL2000 trial, multivariate analysis showed that only ASCT and period of progression/relapse affected event-free survival and OS.[13] In keeping with other authors, this study suggests that the optimal timing of autologous transplantation for patients with FL is early in second or third remission.[24,25]

The 8-year follow-up in this trial documents the safety of rituximab peri and post HDC-ASCT. In common with those of other studies, our results confirm that in vivo purging with rituximab did not adversely affect engraftment, and hematopoietic recovery was not compromised. Rituximab did not seem to add to peri–HDC-ASCT toxicity, as evidenced by comparable toxicities through the autograft period regardless of whether patients received rituximab. Rituximab may cause immunosuppression through several mechanisms, including delayed-onset cytopenia, particularly neutropenia.[26-28] Even though rituximab in this study was administered early after engraftment, and despite the prolonged reduction in immunoglobulin levels in the M+ group, there was no significant increase in toxicity, such as infection or late cytopenia. No increase in the incidence of histologic transformation was reported in the trial. The rate of secondary malignancy in this heavily treated population seemed low and comparable to levels reported in nontransplanted patients.[29,30]

Taken together, this trial shows for the first time to our knowledge that rituximab maintenance therapy for up to 8 months can be safely administered after HDC-ASCT, thereby prolonging PFS. Furthermore, our results support the role of HDC-ASCT as consolidation therapy at first chemosensitive relapse/progression for patients with FL, providing long-term durable remissions in a subset of patients. Thus, both therapies should be incorporated into future trials aimed at improving outcome for patients with relapsed FL. Open questions include the efficacy of rituximab induction before HDC-ASCT and maintenance therapy in patients who have previously received rituximab, the optimal duration of rituximab maintenance therapy, and the optimal schedule of rituximab maintenance.

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.
Employment or Leadership Position: None **Consultant or Advisory Role:** Norbert Schmitz, Roche (C); Herve Tilly, Roche (C); Jan A. Walewski, Mundipharma (C), Celgene (C), Janssen-Cilag (C); Isabelle Bence-Bruckler, Roche (C); Christian H. Geisler, Roche (C), GlaxoSmithKline (C); Christian J. Taverna, Roche (C), Janssen-Cilag (C), Celgene (C) **Stock Ownership:** None **Honoraria:** Ruth Pettengell, Roche; Norbert Schmitz, Roche; Jan A. Walewski, Roche, Mundipharma, Celgene; Isabelle Bence-Bruckler, Roche; Eva Kimby, Roche **Research Funding:** Norbert Schmitz, Roche; Christian Gisselbrecht, Roche; William N. Patton, Roche; Jan A. Walewski, Roche, Mundipharma, GlaxoSmithKline; Isabelle Bence-Bruckler, Roche; Christian H. Geisler, Roche; Eva Kimby, Roche **Expert Testimony:** None **Other Remuneration:** Jan A. Walewski, Roche, Celgene, Genzyme

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Appendix

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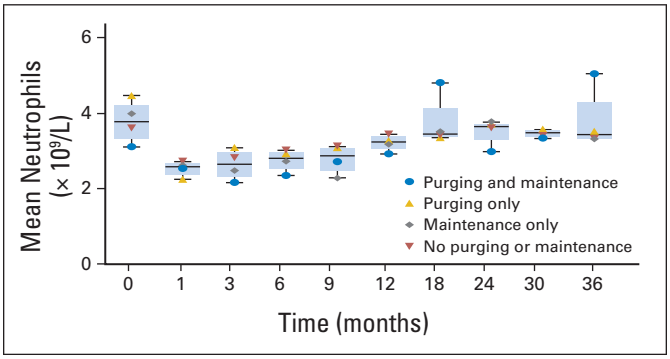

Fig A1. Box-and-whisker plot of mean neutrophil count by treatment group over time. The horizontal line within each box represents the median. The box extends from the 25th to 75th percentile of the data (the interquartile range).