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ORIGINAL REPORT

Rituximab Maintenance Therapy After Autologous Stem-Cell Transplantation in Patients With Relapsed CD20$^+$ Diffuse Large B-Cell Lymphoma: Final Analysis of the Collaborative Trial in Relapsed Aggressive Lymphoma

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ABSTRACT

Purpose
The standard treatment for relapsed diffuse large B-cell lymphoma (DLBCL) is salvage chemotherapy followed by high-dose therapy and autologous stem-cell transplantation (ASCT). The impact of maintenance rituximab after ASCT is not known.

Patients and Methods
In total, 477 patients with CD20$^+$ DLBCL who were in their first relapse or refractory to initial therapy were randomly assigned to one of two salvage regimens. After three cycles of salvage chemotherapy, the responding patients received high-dose chemotherapy followed by ASCT. Then, 242 patients were randomly assigned to either rituximab every 2 months for 1 year or observation.

Results
After ASCT, 122 patients received rituximab, and 120 patients were observed only. The median follow-up time was 44 months. The 4-year event-free survival (EFS) rates after ASCT were 52% and 53% for the rituximab and observation groups, respectively ($P = .7$). Treatment with rituximab was associated with a 15% attributable risk of serious adverse events after day 100, with more deaths (six deaths *v* three deaths in the observation arm). Several factors affected EFS after ASCT ($P < .05$), including relapsed disease within 12 months (EFS: 46% *v* 56% for relapsed disease after 12 months), secondary age-adjusted International Prognostic Index (saaIPI) more than 1 (EFS: 37% *v* 61% for saaIPI < 1), and prior treatment with rituximab (EFS: 47% *v* 59% for no prior rituximab). A significant difference in EFS between women (63%) and men (46%) was also observed in the rituximab group. In the Cox model for maintenance, the saaIPI was a significant prognostic factor ($P < .001$), as was male sex ($P = .01$).

Conclusion
In relapsed DLBCL, we observed no difference between the control group and the rituximab maintenance group and do not recommend rituximab after ASCT.

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INTRODUCTION

The addition of the anti-CD20 monoclonal antibody rituximab to various chemotherapies[1-3] has dramatically improved the response rates in diffuse large B-cell lymphoma (DLBCL) and has resulted in complete responses (CRs) in 75% to 80% of patients. The use of rituximab in first-line treatment improves the overall survival (OS), the 5-year event-free survival (EFS) from 29% to 47% in older patients (60 to 80 years),[4] and the 3-year EFS from 59% to 79% in younger patients (18 to 60 years).[5] However, patients with a poor International Prognostic Index (IPI) require more effective treatment options because they have an unsatisfactory CR rate and a high relapse rate.[6,7] In patients who do not achieve a CR or who experience relapse but remain sensitive to salvage chemotherapy, the therapy should be consolidated with high-dose therapy (HDT) and autologous stem-cell transplantation (ASCT).[8] Even in

the rituximab era,[9] only 10% of these patients obtain long-term disease-free survival with salvage chemotherapy alone.[10] The addition of rituximab to second-line chemotherapy followed by ASCT significantly improves progression-free survival (PFS) in patients who do not receive rituximab in their first-line treatment.[11]

Maintenance treatment has been used successfully in relapsed follicular lymphoma.[12] Furthermore, maintenance treatment after ASCT showed some encouraging results in refractory DLBCL,[13,14] but a randomized study in first-line treatment revealed no significant survival advantage.[15]

The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study was organized among 12 countries. In this study, patients with refractory or relapsed CD20$^+$ DLBCL were randomly assigned to either rituximab, ifosfamide, carboplatin, and etoposide (R-ICE)[16] or rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP).[17] Patients who responded to the chemotherapy were submitted to HDT and ASCT. The initial results[18] revealed no significant difference in outcome between the two regimens. However, several factors did affect survival, including early relapse (< 12 months), the IPI at relapse, and prior exposure to rituximab. The results of the post-transplantation part of the trial, comparing rituximab treatment every 2 months for 1 year with observation alone, and the factors that influenced patient outcome are reported herein.

PATIENTS AND METHODS

This study was a phase III, multicenter, randomized trial that compared the efficacy of R-ICE and R-DHAP in patients with previously treated DLBCL followed by ASCT with or without rituximab maintenance therapy. There were two separate random assignments for salvage therapy and maintenance treatment after transplantation.[18] The present report focuses on the primary end point for the maintenance phase.

Patients were stratified according to participating country, prior rituximab treatment, and relapse within 12 months of diagnosis. The primary end point was EFS, and the secondary end points included response rate, PFS, OS, and toxicities. To detect a 15% change in the 2-year EFS after ASCT in the maintenance therapy arm (65%) versus no maintenance therapy (50%) and to provide an 80% power at the overall 5% (two-sided) significance level, power analyses revealed that 240 patients who underwent ASCT were required for a 1:1 random assignment into two treatment groups over 3 years and that they should be observed for a minimum of 2 years. The expected number of events during a 5-year period was 140 events. This sample size takes drop-out rates as a result of the salvage treatment and transplantation procedure into account. Initially, we expected a 40% drop-out rate, but this estimate was adjusted to 50% after the first interim analysis of 200 patients. As suggested by the data monitoring committee in May 2007, the initial sample size was amended from 400 to 480 participants to maintain the planned power with 240 patients (Data Supplement).

This study was designed by the steering committee of CORAL and approved by the relevant institutional review boards or ethics committees. All patients gave written informed consent. The study is registered under EUDRACT No. 2004-002103-32 and ClinicalTrials.gov NCT00137995.

Patients

In brief, the CORAL study included patients 18 to 65 years old with aggressive CD20$^+$ B-cell lymphoma, including DLBCL with relapse or patients who did not achieve CR using a standard anthracycline-based (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen. All patients underwent histologic confirmation of CD20$^+$ aggressive B-cell lymphoma before enrollment. Eligible patients had a WHO performance status of 0 to 1. Exclusion criteria included CNS involvement, history of HIV infection, post-transplantation lymphoproliferative disorder, and inadequate organ function. Patients were fully evaluated, including computed tomography (CT) scanning of the thorax and abdomen and bone marrow biopsy. The secondary age-adjusted IPI (saaIPI) was determined according to the absence or presence of risk factors, poor performance status, elevated lactate dehydrogenase, and disseminated stage before salvage treatment.[19,20] Patient enrollment occurred between July 2003 and June 2008, and the last patient was randomly assigned in the maintenance phase of the study in October 2008. In total, 481 patients were randomly assigned to the R-ICE arm (n = 243) or the R-DHAP arm (n = 234; Fig 1). A total of 255 patients who achieved CR (n = 142), partial response (PR; n = 92), or stable disease (n = 7) after the third cycle of salvage treatment received consolidation with ASCT, and 242 patients received maintenance rituximab (n = 122) or observation (n = 120; Fig 1).

Patient characteristics at the second random assignment are listed in Table 1. Patient characteristics at entry for all patients are provided in the Data Supplement. No significant differences between the two arms were observed. Histologic materials were reviewed by local hematopathologists in the participating centers. An international central review was performed in 69% of the patients, and 18 patients were not reviewed as having DLBCL (two patients had follicular lymphoma grade 3, five patients had follicular lymphoma grade 2, two patients had T-cell lymphoma, two patients had Hodgkin lymphoma, and seven patients remained unclassified).

Treatment

Details of the treatment and monitoring have been published previously.[18] Briefly, only chemotherapy-sensitive patients (CR, unconfirmed CR [CRu], or PR) after three cycles of R-ICE[16] or R-DHAP[17] received a consolidation with high-dose chemotherapy carmustine, etoposide, cytarabine, and melphalan (BEAM) followed by ASCT. These patients were randomly assigned to groups with or without rituximab maintenance therapy (375 mg/m^2 every 8 weeks for 1 year) on day 28 after ASCT (Fig 2).

Radiotherapy after transplantation was not performed, and it was considered as an event. Supportive treatments were administered according to the standard use in each center.

Assessment of Response and Follow-Up

Response was assessed using conventional diagnostic methods, including CT scanning after the third chemotherapy course. Positron emission tomography scans were not mandatory, and bone marrow biopsies were repeated only if the samples were observed to be abnormal before treatment.

Response was assessed using the International Working Group criteria.[21] CR was defined as the disappearance of all documented disease, and CRu was used in cases of residual mass. PR included a 50% reduction in measurable disease. Follow-up procedures included a physical examination every 3 months for the first year with a complete evaluation at the end or at an earlier time point if clinically indicated. Follow-up procedures were performed every 6 months for 2 years thereafter, and thoracic and abdominal CT scans were performed annually.

Statistical Analysis

Analyses were first performed following the intent-to-treat principle. EFS was defined as the time from treatment initiation to progression, relapse, new treatment, or death by any cause, whichever occurred first. It was considered an event if patients received alternative treatment outside of the protocol. PFS was defined as the time from study entry until disease progression or death by any cause. OS was defined as the time from treatment initiation to death by any cause.

Survival functions were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses

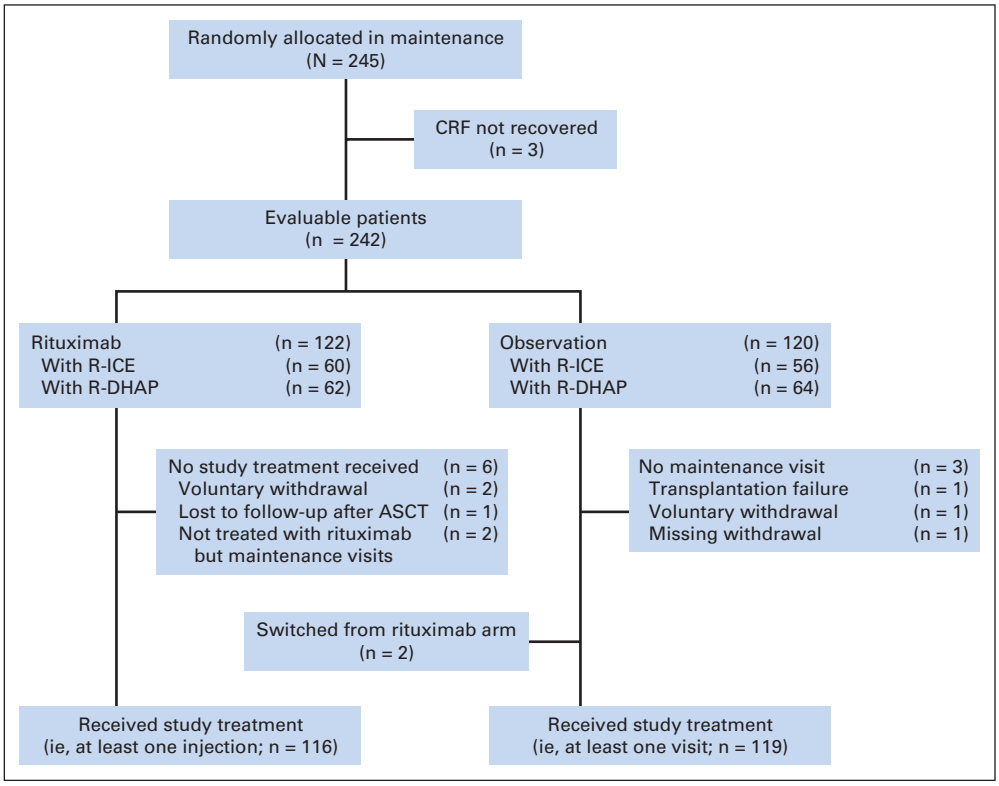

Fig 1. CONSORT diagram of the patient distribution according to the treatment arm resulting from the second random assignment. ASCT, autologous stem-cell transplantation; CRF, case report forms; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide.

were performed using a Cox proportional hazards model. Differences between the results of comparative tests were considered significant if the two-sided $P < .05$. All statistical analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC).

RESULTS

Response to Treatment

The overall response rate (CR + CRu + PR) after salvage chemotherapy and before transplantation was 63% in the R-ICE group and 64% in R-DHAP group, with 142 patients (58%) experiencing CR or CRu and 92 patients (38%) exhibiting PR before ASCT. For patients with prior exposure to rituximab and progression within 12 months of diagnosis, the overall response rate was 46% (Data Supplement).

A total of 245 patients received BEAM and ASCT, and 242 evaluable patients were randomly assigned to either the treatment group (Fig 2, Table 1) with rituximab or the observation-only group. In the treatment group, 78 patients (67%) received all six cycles; new progression of the disease was the primary reason for patients not completing the full treatment. At the end of the maintenance therapy, the CR rates were 57% and 50% for the rituximab and observation groups, respectively, including all deaths.

Survival

After a median follow-up of 44 months for the 469 patients who were enrolled, no difference was detected between the treatment and control arms of the study. The 4-year OS was 43% (95% CI, 36% to 50%) for the R-ICE arm and 51% (95% CI, 44% to 58%) for the R-DHAP arm ($P = .3$). The EFS was 26% (95% CI, 20% to 32%) in the R-ICE arm and 34% (95% CI, 36% to 50%) in the R-DHAP arm ($P = .2$; Appendix Figs A1A and A1B, online only).

Considering only patients who received ASCT and were randomly assigned to the maintenance arm after ASCT, the 4-year EFS was 52% (95% CI, 42% to 61%) in the rituximab group and 53% (95% CI, 44% to 62%) in the observation group ($P = .7$; Fig 3A). We observed no difference in the PFS ($P = .8$) or OS between the rituximab group and the observation group (Table 2). We also observed no significant difference between the patients who achieved CR or PR before ASCT (Table 2, Fig 3B).

The 4-year EFS, PFS, and OS after ASCT were affected by a number of factors, including prior treatment with rituximab, early relapse, and saaIPI (Table 2, Figs 3C and 3D). However, the Cox model revealed that only an saaIPI of 2 to 3 remained significant ($P < .001$) for the EFS, PFS, and OS. Men performed significantly poorer than women (Table 2), a finding that was related to the superior survival of women in the rituximab group (Figs 4A to 4C). Additional subset analyses are included in the Data Supplement. In the multivariate analyses of PFS, male sex ($P = .01$) and saaIPI ($P < .001$) remained significant prognostic factors. Treatment arm, early relapse, prior rituximab exposure, and PR were no longer significant factors (Data Supplement). However, in a subset analysis based on sex that compared the rituximab and observation groups, the 3-year EFS was 43% (95% CI, 31% to 54%) in men and 69% (95% CI, 53% to 81%) in women ($P = .1$; Data Supplement).

Relapse and Progression

The first progression or relapse was observed in 47 and 46 patients in the rituximab and observation groups, respectively, primarily

Table 1. Baseline Demographic and Clinical Characteristics of the Patients Randomly Assigned for Maintenance (Intent to Treat)

Characteristic	Rituximab (n = 122)	Observation (n = 120)	*P*
Age, years			
Median	54	54	
Range	19-65	19-65	
< 40	17	22	NS
Sex			
Male	76	83	
Female	46	37	NS
Body mass index, kg/m^2			
Median	25.8	26.7	NS
Range	17.3-36.8	18.3-45.2	
> 30	21	28	
Ann Arbor stage			
I-II	53	48	
III-IV	69	71	NS
Extranodal site > 1	30	30	NS
Bone marrow involvement	13	8	NS
Elevated LDH	54	51	NS
Response after salvage therapy			
CR + CRu	73	69	NS
PR	47	45	
Stable disease	2	5	
saaIPI at relapse			
0-1	84	81	
2-3	36	36	NS
Time to relapse, months			
< 12*	33	41	NS
≥ 12	89	76	
Prior rituximab treatment	63	62	NS
Prior CHOP-like first-line chemotherapy	102	100	NS
Salvage regimen			
R-ICE	60	56	
R-DHAP	62	64	

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CRu, uncertain complete response; LDH, lactate dehydrogenase; NS, not significant; PR, partial response; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; saaIPI, secondary age-adjusted International Prognostic Index.
*Including patients not achieving CR in first-line treatment.

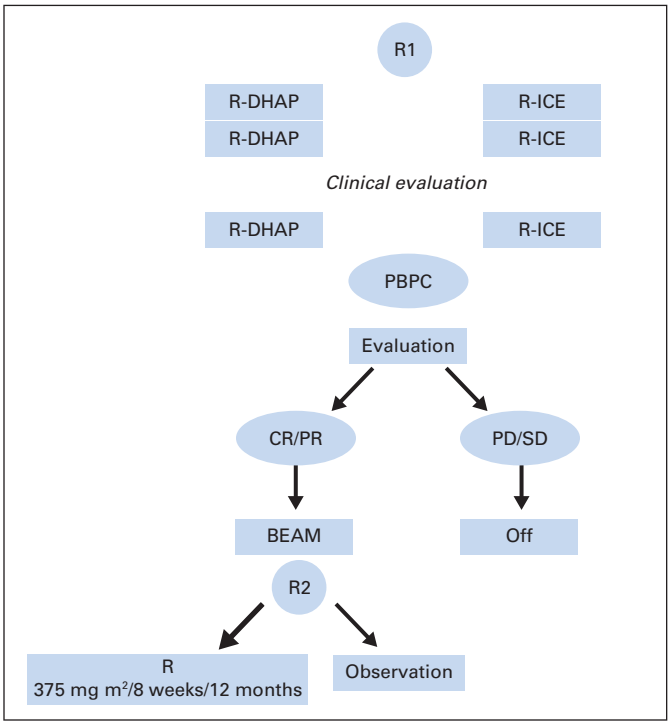

Fig 2. Treatment protocol. BEAM, carmustine, etoposide, cytarabine, melphalan; CR, complete response; PBPC, peripheral-blood progenitor cells; PD, progressive disease; PR, partial response; R, rituximab; R1, first random assignment; R2, second random assignment; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; SD, stable disease.

during the follow-up period. Although this occurrence was at the initial site, half included a new site of involvement. These patients underwent various additional treatments, including radiotherapy (25%) and chemotherapy (76%) with transplantation (14 allografts; Data Supplement). A second CR was observed in 21 patients and a PR in 13 patients.

The majority of deaths were a result of lymphoma. Forty-three deaths occurred in the rituximab group, and 17 of these deaths occurred within 1 year after the transplantation. Thirty-eight deaths occurred in the observation group, and 19 occurred within 1 year after ASCT.

Adverse Events

The treatment was well tolerated, and the reported events were separated into those that occurred before day 100 after ASCT and those that occurred after day 100. A total of 87 adverse events (AEs) were reported in 54 patients (47%) within 100 days in the rituximab group, whereas 75 AEs were reported in 50 patients (42%) in the observation group. A total of 75 AEs were reported in 35 patients (30%) in the rituximab group more than 100 days after ASCT, whereas 24 AEs were observed in 20 patients (17%) in the observation group. The majority of the AEs were infections; 45 episodes of infection were reported in the rituximab group, and 13 episodes were reported in the observation group. Grade 3 or greater delayed neutropenia after day 100, excluding values after additional treatment, was reported in 11 patients (9%) in the rituximab group and in seven patients (6%) in the observation group.

Forty-three serious AEs (SAEs) were reported in the rituximab group, and 22 SAEs were reported in the observation group. After day 100, 23 SAEs were reported in the rituximab arm, and only five were reported in the observation group. Fatal outcomes were observed in six patients in the rituximab group and three patients in the observation group; four deaths resulted from secondary cancers (two in the rituximab group and two in the observation group), one death resulted from varicella and one death resulted from myocarditis several months after the end of the treatment, and three deaths resulted from infections and pneumonia.

DISCUSSION

The present results demonstrate a similar response rate of 63% for the two initial chemotherapy regimens over a 4-year follow-up, but only 37% of the patients attained CR. In addition, only 51% of patients were able to undergo ASCT. We did not observe a difference in the

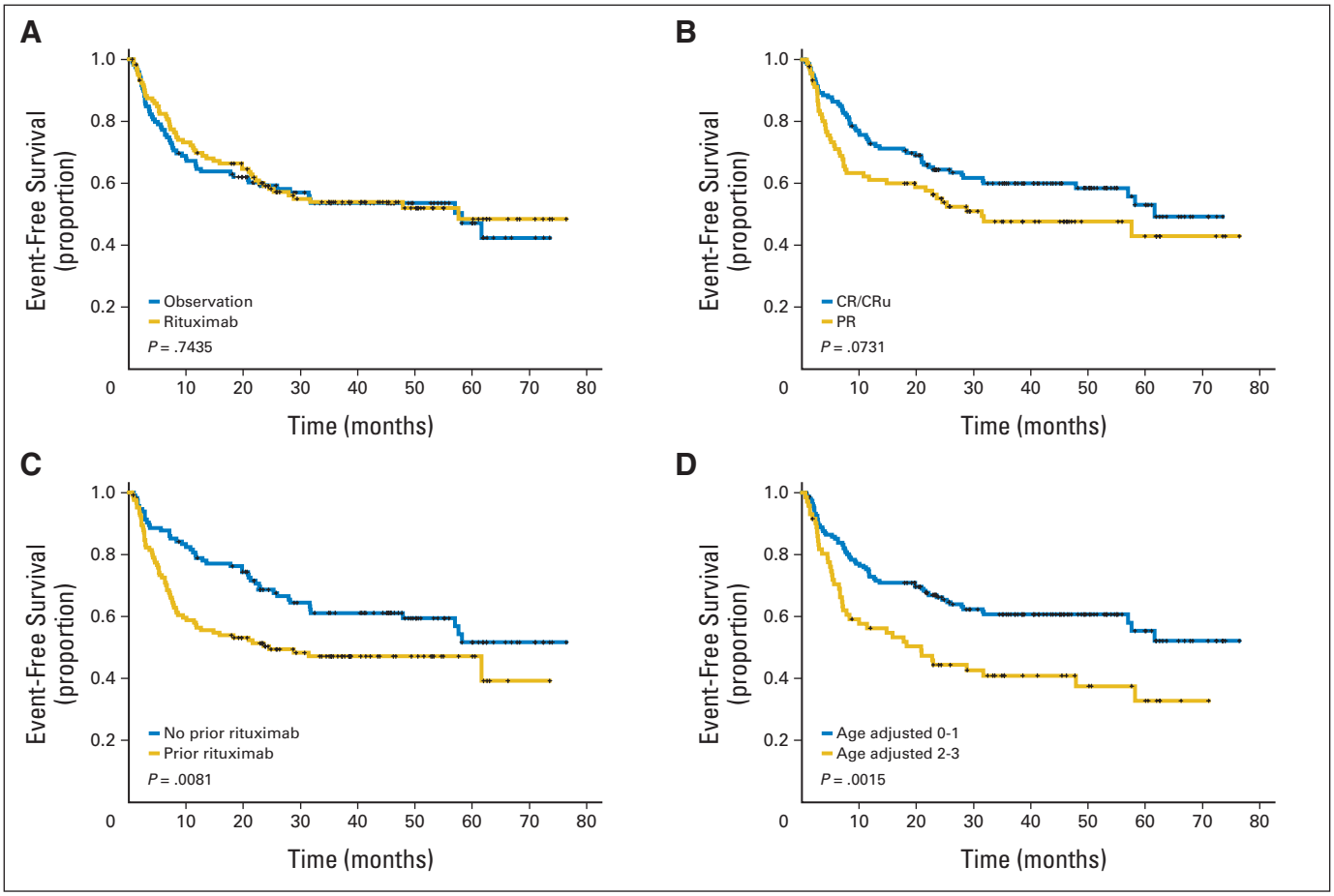

Fig 3. Survival of patients after autologous transplantation. (A) Event-free survival (EFS) according to the second random assignment and treatment arm of rituximab (n = 122) or observation (n = 120). (B) EFS at the second random assignment according to disease status before transplantation (complete response [CR] plus unconfirmed CR [CRu], n = 142; partial response [PR], n = 92). (C) EFS at the second random assignment according to prior rituximab exposure (n = 125) or no prior rituximab (n = 117) during first-line treatment. (D) EFS at the second random assignment according to age-adjusted International Prognostic Index at relapse of 0 to 1 (n = 165) versus 2 to 3 (n = 72).

survival rates between the two treatment regimens after ASCT. In the multivariate analysis for maintenance, the hazard ratio for R-ICE was 1.47 (95% CI, 0.98 to 2.2; $P = .06$). This trend of an improved outcome for R-DHAP (Appendix Fig A1) may reflect the observed preference for the germinal center B subtype for this regimen in the subset analysis.[22]

The objective of the second part of this study was to test the hypothesis that rituximab treatment after transplantation would reduce the relapse rate in these patients. Although patients who received HDT with BEAM and ASCT were randomly assigned to either rituximab or the observation group, no difference was observed between these two groups (Fig 3). However, the toxicity was increased by 15% in reported SAEs in the rituximab arm after day 100 after ASCT, with an excess of deaths by infections that was most likely related to immunodeficiency. Only 10% of patients in the rituximab-treated group experienced delayed neutropenia, which was not significantly different from patients in the observation arm. Maintenance rituximab therapy after ASCT has been evaluated over different durations and treatment strategies, but it has been primarily examined in the context of short treatment courses administered soon after transplantation.[13-15] The increase in toxicity that was observed after this treatment raises concerns about prolonging immunodeficiency after ASCT and leads us to propose only 1 year of treatment, rather than the 2 years of treatment recommended in cases of follicular lymphoma.

This first randomized study does not support the promising results that had been described in two phase II studies after ASCT.[13,14] These results are consistent with our randomized study of high-risk DLBCL where 269 patients were randomly assigned to either an observation-only control group or a treatment group who received 4 weekly injections of rituximab after transplantation,[15] which found that rituximab treatment lacked efficacy. These results are also consistent with those of the Intergroup study,[3] which reported that maintenance therapy had no impact on patients who had previously been exposed to rituximab. The duration of the maintenance therapy does not explain these results because 50% of the relapses after ASCT occurred during the maintenance period. Rituximab alone has limited activity in DLBCL, and its role is mostly related to chemotherapy sensitization of the lymphoma by different mechanisms that are not completely understood.[23]

The previously described factors that affected the outcome of patients who received transplantation were also identified in our univariate analysis (Table 2). The saaIPI score was the only significant variable that was associated with male sex in the multivariate analyses.

Table 2. Prognostic Factors at the Second Random Assignment

Patients	No. of Patients	4-Year EFS (%)	*P*	4-Year PFS (%)	*P*	4-Year OS (%)	*P*
Arm			.7		.8		.7
Rituximab	122	52		52		61	
Observation	120	53		56		65	
R-ICE			.4		.5		.4
Rituximab	60	50		50		61	
Observation	56	47		49		53	
R-DHAP			.7		.4		.2
Rituximab	62	55		55		62	
Observation	64	59		63		77	
Prior rituximab			.009		.03		.03
Yes	125	47		50		58	
No	117	59		59		69	
Treatment failure, months			.04		.1		.07
< 12	105	48		51		59	
≥ 12	137	56		56		66	
saaIPI			.0018		< .001		< .001
0-1	165	61		63		72	
2-3	72	37		37		45	
Response			.07		.2		.3
CR + CRu	142	58		58		66	
PR	92	48		51		59	
Sex			.01		.01		.007
Male	159	46		48		55	
Female	83	63		65		75	
Rituximab arm			.005		.005		.009
Male	76	38		48		50	
Female	46	70		70		76	
Observation arm			.5		.6		.3
Male	83	53		56		60	
Female	37	56		59		77	

Abbreviations: CR, complete response; CRu, unconfirmed complete response; EFS, event-free survival; OS, overall survival; PFS, progression-free survival; PR, partial response; R-DHAP, rituximab dexamethasone, cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; saaIPI, secondary age-adjusted International Prognostic Index.

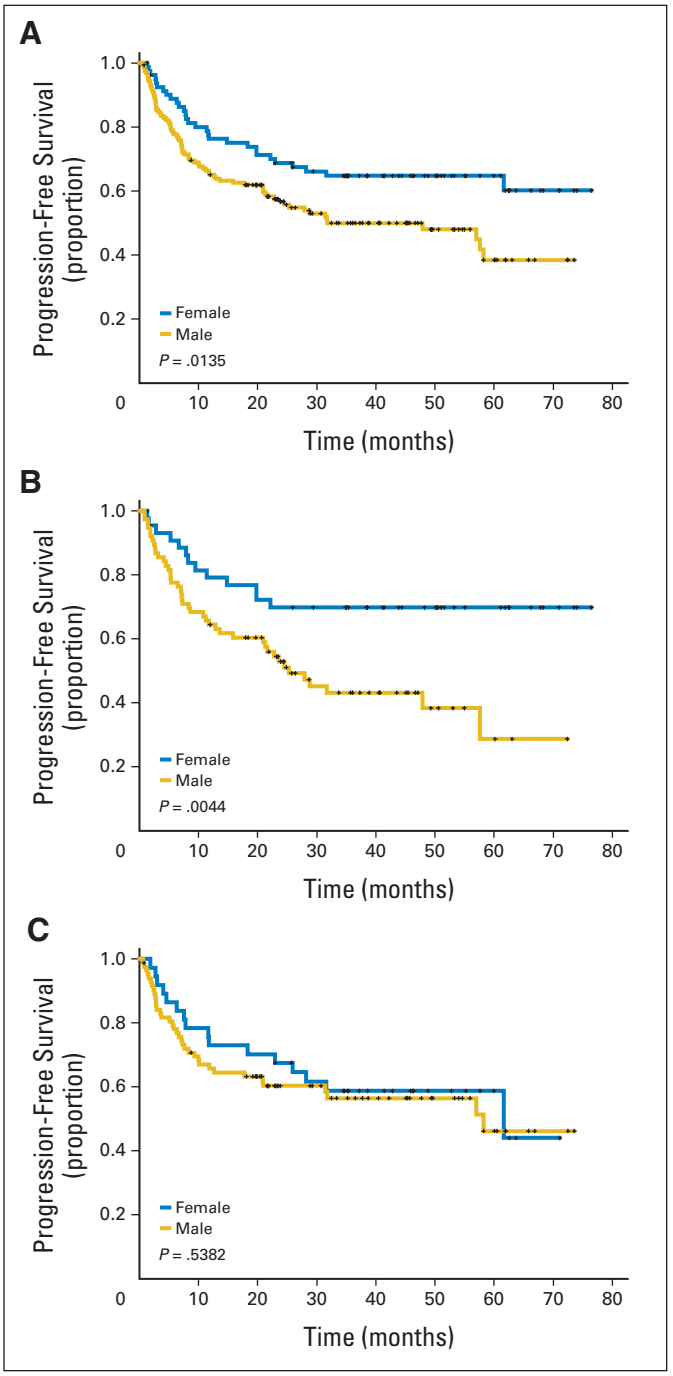

Fig 4. Survival of patients after autologous transplantation according to sex. (A) Progression-free survival (PFS) at the second random assignment according to male (n = 159) or female (n = 83) sex. (B) PFS at the second random assignment according to male (n = 78) or female (n = 46) sex and the rituximab treatment arm. (C) PFS at the second random assignment according to male (n = 83) or female (n = 37) sex and observation.

Male sex is an adverse prognostic factor in follicular lymphomas and DLBCL in the rituximab era.[24,25] One striking observation in the present study was the significant survival difference between women and men who received rituximab maintenance therapy. This disparity cannot be explained by the underlying sex-related mortality hazard (ie, the natural 5- to 10-year survival advantage of women over men in the general population) because no such sex difference was observed in the observation arm. A higher rituximab clearance in males, which results in lower rituximab exposure, has been reported previously.[24] These results are similar to the findings of Ng et al[26] in a population approach examining the outcome of rituximab in patients with rheumatoid arthritis. These investigators also observed a 39% greater clearance of rituximab in men than in women. In our study, the impact of rituximab was obscured in overweight postmenopausal women who presented higher testosterone levels as a result of hyperinsulinism.[27] Therefore, we hypothesize that the lower survival impact of rituximab that we observed in males may be a result of hormone-related pharmacokinetic variations. Thus, the impact of an increased dose of rituximab on survival requires further investigation using randomized studies.

Our data are surprising because no other drugs were involved after ASCT. The role of rituximab in DLBCL requires further analysis, as does the role of sex, in large randomized studies with or without rituximab maintenance.

In summary, rituximab maintenance therapy does not prevent relapse after ASCT and was associated with higher toxicity. Therefore,

this treatment is not recommended in relapsed DLBCL. The initial prognostic parameters still apply for patients who receive transplantation. The patient population in this study is representative of patients who will require innovative approaches to treatment in the future.[28] Consequently, new drugs that are designed to increase the response rate of salvage regimens and novel approaches, including allogeneic transplantation, should be explored.[29-31] An improved understanding of the biology of DLBCL derived at least in part from studies of patient tumor specimens[22] will play a key role in the development of novel targeted therapies for this disease.

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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Final approval of manuscript: All authors

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