ASBMT American Society for Blood and Marrow Transplantation

Impact of Pre-transplant Rituximab on Survival after Autologous Hematopoietic Stem Cell Transplantation for Diffuse Large B Cell Lymphoma

Timothy S. Fenske,[1] Parameswaran N. Hari,[2] Jeanette Carreras,[2] Mei-Jie Zhang,[2] Rammurti T. Kamble,[3] Brian J. Bolwell,[4] Mitchell S. Cairo,[5] Richard E. Champlin,[6] Yi-Bin Chen,[7] César O. Freytes,[8] Robert Peter Gale,[9] Gregory A. Hale,[10] Osman Ilhan,[11] H. Jean Khoury,[12] John Lister,[13] Dipnarine Maharaj,[14] David I. Marks,[15] Reinhold Munker,[16] Andrew L. Pecora,[17] Philip A. Rowlings,[18] Thomas C. Shea,[19] Patrick Stiff,[20] Peter H. Wiernik,[21] Jane N. Winter,[22] J. Douglas Rizzo,[2] Koen van Besien,[23] Hillard M. Lazarus,[24] Julie M. Vose[25]

Incorporation of the anti-CD20 monoclonal antibody rituximab into front-line regimens to treat diffuse large B cell lymphoma (DLBCL) has resulted in improved survival. Despite this progress, however, many patients develop refractory or recurrent DLBCL and then undergo autologous hematopoietic stem cell transplantation (AuHCT). It is unclear to what extent pre-transplant exposure to rituximab affects outcomes after AuHCT. Outcomes of 994 patients receiving AuHCT for DLBCL between 1996 and 2003 were analyzed according to whether rituximab was (n = 176; +R cohort) or was not (n = 818; −R cohort) administered with front-line or salvage therapy before AuHCT. The +R cohort had superior progression-free survival (PFS; 50% vs 38%; $P = .008$) and overall survival (OS; 57% vs 45%; $P = .006$) at 3 years. Platelet and neutrophil engraftment were not affected by exposure to rituximab. Nonrelapse mortality (NRM) did not differ significantly between the 2 cohorts. In multivariate analysis, the +R cohort had improved PFS (relative risk of relapse/progression or death, 0.64; $P < .001$) and improved OS (relative risk of death, 0.74; $P = .039$). We conclude that pre-transplant rituximab is associated with a lower rate of progression and improved survival after AuHCT for DLBCL, with no evidence of impaired engraftment or increased NRM.

Biol Blood Marrow Transplant 15: 1455-1464 (2009)

KEY WORDS: Autologous hematopoietic stem cell transplantation, Lymphoma, Rituximab

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common form of aggressive non-Hodgkin lymphoma (NHL). The probability of being cured by the initial treatment is predicted by the International Prognostic Index (IPI), which accounts for age, performance status, tumor stage, lactate dehydrogenase (LDH) level, and

From the [1]Medical College of Wisconsin, Milwaukee, Wisconsin; [2]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin; [3]Baylor College of Medicine, Houston, Texas; [4]Cleveland Clinic Foundation, Cleveland, Ohio; [5]New York Presbyterian Hospital, New York, New York; [6]M.D. Anderson Cancer Center, Houston, Texas; [7]Massachusetts General Hospital, Boston, Massachusetts; [8]South Texas Veterans Health Care System, University of Texas Health Science Center, San Antonio, Texas; [9]Celgene Corporation, Summit, New Jersey; [10]All Children's Hospital, St. Petersburg, Florida; [11]Ibni Sina Hospital, Ankara, Turkey; [12]Emory University, Winship Cancer Institute, Atlanta, Georgia; [13]The Western Pennsylvania Hospital, Pittsburgh, Pennsylvania; [14]South Florida Bone Marrow Stem Cell Transplant Institute, Boynton Beach, Florida; [15]United Bristol Healthcare, Bristol, UK; [16]Louisiana State University Medical Center, Shreveport, Louisiana; [17]Hackensack University Medical Center, Hackensack, New Jersey; [18]Calvary Mater Newcastle Hospital, University of Newcastle, Newcastle, Australia; [19]University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [20]Loyola University Health System, Maywood, Illinois; [21]Montefiore Medical Center-North Division, and New York Medical College, Bronx, New York; [22]Northwestern Memorial Hospital, Chicago, Illinois; [23]University of Chicago Medical Center, Chicago, Illinois; [24]University Hospitals Case Medical Center, Cleveland, Ohio; [25]University of Nebraska Medical Center, Omaha, Nebraska.

Financial disclosure: See Acknowledgments on page 1463.

Correspondence and reprint requests: Timothy S. Fenske, MD, Division of Neoplastic Diseases, Medical College of Wisconsin, 9200 W Wisconsin Avenue, Milwaukee, WI 53226 (e-mail: tfenske@mcw.edu).

Received May 20, 2009; accepted July 19, 2009

1083-8791/09/1511-0014$36.00/0
doi:10.1016/j.bbmt.2009.07.017

number of sites of extranodal disease as prognostic variables [1]. Before the introduction of rituximab, the probability of long-term survival ranged between 26% and 73%, depending on the IPI [1]. With the addition of rituximab to standard front-line chemotherapy, outcomes have improved across all IPI groups [2-5].

For patients with relapsed chemosensitive DLBCL, the Parma trial established high-dose chemotherapy and autologous hematopoietic cell transplantation (AuHCT) as superior to conventional salvage chemotherapy alone [6]. However that study was carried out in the prerituximab era, making its relevance in DLBCL patients treated with rituximab-containing frontline or salvage regimens uncertain. It has been reported that pre-transplant rituximab exposure may affect outcomes after high-dose therapy and AuHCT. For example, in one single-center retrospective study, inclusion of rituximab in pre-transplant salvage therapy was associated with improved survival and delayed platelet engraftment in patients with intermediate-grade B cell NHL undergoing AuHCT [7].

We hypothesized that pre-transplant exposure to rituximab may affect outcomes after AuHCT for DLBCL, including relapse/progression, survival, toxicity, and engraftment. Using the Center for International Blood and Transplant Research (CIBMTR) database, we retrospectively compared outcomes in rituximab-naïve and rituximab-exposed adult patients undergoing AuHCT for DLCBL.

PATIENTS AND METHODS

Data Sources

A research affiliate of the International Bone Marrow Transplant Registry, the Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program (NMDP), the CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplantations to a statistical center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee or the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all consecutive transplantations; compliance is monitored by onsite audits. Subjects are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. CIBMTR observational studies are conducted with a waiver of informed consent and in compliance with HIPAA regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

The CIBMTR collects data at 2 levels: registration and research. Registration data include disease type, age, sex, pre-transplant disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow [BM]– and/or blood-derived stem cells), high-dose conditioning regimen, posttransplantation disease progression and survival, development of a new malignancy, and cause of death. Requests for data on progression or death for registered patients are made at 6-month intervals. All CIBMTR teams contribute registration data. Research data are collected on a subset of registered patients selected using a weighted randomization scheme and include detailed disease and pre-transplant and posttransplantation clinical information.

Patients

A total of 1155 patients who underwent AuHCT for DLBCL between 1996 and 2003 were reported to the CIBMTR database. Eight patients aged < 18 years at transplantation and 11 patients receiving posttransplantation rituximab for maintenance were excluded. Seventy-four patients who relapsed > 10 years after initial diagnosis, 56 patients with bone marrow grafts, and 12 patients who received rituximab as part of the conditioning regimen also were excluded. Thus, a total of 994 subjects were evaluated. Of these subjects, 176 received rituximab before transplantation, as part of first-line therapy and/or salvage therapy (the +"R" cohort), while 818 were rituximab-naïve at the time of transplantation (the −"R" cohort).

Study Endpoints

Outcomes analyzed included engraftment, nonrelapse mortality (NRM), relapse/progression, progression-free survival (PFS), and overall survival (OS). NRM was defined as death occurring within 28 days posttransplantation or death without progression of lymphoma. Subjects with lymphoma progression were censored at the time of progression, and a cumulative incidence estimate was derived, with progression or relapse as the competing risk. Progression/relapse was defined as progressive lymphoma at $\geq$ 28 days posttransplantation or recurrence of lymphoma. It could follow a period of "stable" disease posttransplantation or a partial remission (PR) or complete remission (CR). Progression/relapse represents new or larger areas of lymphoma ($\geq$ 25% increase in largest diameter) compared with the best posttransplantation lymphoma state. Relapse/progression was summarized by the cumulative incidence estimate, with NRM as the competing risk. For PFS, subjects were considered treatment failures at the time of lymphoma progression or death from any cause. Subjects alive without evidence of lymphoma progression were censored at last follow-up, and the PFS event was summarized by a survival curve. The OS interval variable was defined as time from the date of transplantation to the date of

death or last contact and was summarized by a survival curve.

Statistical Analysis

Subject-, disease-, and transplantation-related variables for the +R and −R cohorts were compared using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate probabilities of neutrophil and platelet recovery and NRM were calculated using cumulative incidence curves to accommodate corresponding competing risks [8]. Probabilities of OS and PFS were calculated using the Kaplan-Meier estimator [9], and 95% confidence intervals (CIs) were calculated with a log-transformation.

To compare the outcomes of NRM, progression/relapse, PFS, and OS, a Cox proportional hazards model was used to adjust for potential imbalance in baseline characteristics between treatment cohorts. A stepwise-forward method was used to identify covariates that influenced outcomes. Each model contained the main effect (rituximab vs no rituximab). Any covariate with a P value $\leq .05$ was considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome; the results indicated that all variables except Karnofsky performance score met the proportional hazards assumption. Cox regression models stratified on the Karnofsky score were used for each outcome event. The final results are expressed as relative risk (RR) of the event and its 95% CI. The following variables were considered in model building: rituximab versus no rituximab (main effect), age at transplantation, Karnofsky performance status at transplantation, number of lines of chemotherapy, BM involvement at transplantation, disease status at transplantation, size of largest lymphoma mass before transplantation, time from diagnosis to transplantation, conditioning regimen, year of transplantation, and administration of granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) within 7 days posttransplantation. The main effect of interest, rituximab versus no rituximab, was retained in all steps of model building. Potential interactions between the main effect and all significant risk factors were tested, with no interactions detected for all significant risk factors. All analyses were performed using SAS version 8.2 (SAS Institute, Cary NC).

RESULTS

Patient Characteristics

Patient-, disease-, and transplantation-related characteristics are summarized in Table 1. A total of 176 subjects received rituximab before transplantation during first-line therapy and/or salvage therapy (the +"R" cohort), and 818 subjects were rituximab-naïve at the time of transplantation (the −"R" cohort). The median follow-up of survivors was 44 months for the +R cohort and 62 months for the −R cohort. Follow-up was 90% complete.

The +R cohort had a higher median age (58 vs 52 years; $P < .001$) and a higher proportion of patients aged 55 or older (55% vs 40%; $P < .001$). The +R cohort also was more heavily pretreated before transplantation, with a higher proportion of patients receiving > 2 lines of chemotherapy (57% vs 40%; $P < .001$); however, this difference may be accounted for to some extent by the fact that rituximab alone was counted as a regimen. Rituximab was administered with first-line chemotherapy in 38% of patients and with salvage therapy only in 62% of patients, with no patients receiving rituximab with both first-line and salvage therapy. The cohorts were well matched for disease status at transplantation, bulky disease, second line age-adjusted IPI score, and BM involvement. In addition, pre-transplant chemosensitivity and Ann Arbor stage at transplant did not differ between the 2 cohorts.

The +R and −R cohorts underwent AuHCT at similar intervals after diagnosis and received similar conditioning regimens. As expected, transplantation was performed between 1999 and 2003 in 96% of the patients in the +R cohort and between 1996 and 2001 in 93% of those in the −R cohort ($P < .001$). A similar proportion of patients in each cohort received myeloid growth factor posttransplantation. The use of posttransplant radiation therapy also was similar in the 2 cohorts.

Outcomes

Engraftment

The cumulative incidence of platelet and neutrophil engraftment at 28 and 100 days was similar in the 2 cohorts (Figure 1). There was no clinically significant difference in the rate of neutrophil engraftment (defined as an absolute neutrophil count [ANC] $> 0.5 \times 10^9$/L) or platelet engraftment (defined as a platelet count of 20,000/μL with no transfusion requirement) between the 2 cohorts. The patients who received rituximab within 3 months of transplantation (n = 60) were analyzed separately for engraftment delay. These patients also achieved neutrophil engraftment by day 17 and had platelet recovery at a median of 17 days, with no difference compared with the −R cohort ($P = .23$) (data not shown).

NRM/causes of death

The cumulative incidences of NRM at 1, 3, and 5 years did not differ significantly between the 2 cohorts ($P = .06$) (Figure 2). In multivariate analysis, older age

Table 1. Patient-, Disease-, and Transplantation Characteristics

Variable	+R Cohort		−R Cohort		
	n Evaluable	n (%)	n Evaluable	n (%)	*P* Value*
Number of patients		176		818	
Age, years, median (range)	176	58 (20-76)	818	52 (18-75)	< .001
Age at transplantation, years	176		818		< .001
< 55		79 (45)		489 (60)	
≥ 55		97 (55)		329 (40)	
Male sex	176	89 (51)	817	473 (58)	.08
Pre-transplant Karnofsky score < 90	166	64 (39)	795	292 (37)	.66
Second line age-adjusted IPI at transplantation	176		818		.27
Low		40 (23)		201 (25)	
Low-intermediate		45 (25)		216 (26)	
High-intermediate		17 (10)		113 (14)	
High		2 (1)		16 (2)	
Missing		72 (41)		272 (33)	
Disease status at transplantation	176		761		.45
CR1		38 (22)		130 (17)	
CR2+		35 (20)		124 (16)	
PIF-sensitive		32 (18)		152 (20)	
PIF-resistant		12 (7)		43 (6)	
Relapse-sensitive		45 (25)		256 (34)	
Relapse-resistant		14 (8)		56 (7)	
Number of previous lines of therapy	176		815		< .001
1		13 (8)		119 (15)	
2		62 (35)		370 (45)	
3		65 (37)		234 (29)	
4		34 (19)		67 (8)	
5		2 (1)		20 (2)	
Timing of rituximab treatment:	176		NA		—
With first-line chemotherapy only		66 (38)			
With salvage therapy only		110 (62)			
Chemosensitive disease at transplantation	173		784		.75
Sensitive		146 (84)		653 (83)	
Marrow involvement at transplantation	172	3 (2)	752	37 (5)	.06
Mass 5cm before transplantation cm	60	16 (27)	274	95 (35)	.23
Disease stage at diagnosis	168		802		.10
I		21 (13)		88 (11)	
II		27 (16)		190 (24)	
III		54 (32)		195 (24)	
IV		66 (39)		326 (41)	
Interval from diagnosis to transplantation, months, median (range)	176	14 (3-200)	818	13 (2-277)	.46
Interval from diagnosis to transplantation, months	176		818		.75
<12		76 (43)		364 (45)	
≥ 12		100 (57)		454 (55)	
Radiation therapy posttransplantation	176	24 (14)	810	124 (15)	.57
Conditioning regimen	176		818		.18
TBI-based		27 (15)		114 (14)	
BEAM and similar		102 (58)		522 (64)	
CBV or similar		27 (15)		77 (9)	
Bu-MEL/Bu-Cy		10 (6)		48 (6)	
Others		10 (6)		57 (7)	
Interval from last rituximab given to transplantation, median (range), months	170	5 (1-34)	NA		—
Graft type	176		818		.47
Peripheral blood		165 (94)		754 (92)	
Bone marrow + PBSCs		11 (6)		64 (8)	
Year of transplantation	176		818		< .001
1996-1998		7 (4)		481 (59)	
1999-2001		80 (45)		281 (34)	
2002-2003		89 (51)		56 (7)	
G-CSF or GM-CSF given within 7 days posttransplantation	176	159 (90)	818	710 (87)	.20
Median follow-up of survivors, months	102	42 (2-83)	336	62 (1-116)	—

NA indicates not applicable; PIF, primary induction failure; TBI, total body irradiation; BEAM, BCNU + etoposite + Ara-C + melphalan; CBV, cyclosphamide + BCNU + VP16; PBSCs, peripheral blood stem cells.
*The χ^2 test was used for discrete covariates; the Kruskal-Wallis test was used for continuous covariates.

(≥ 55 years; RR = 1.79; $P < .001$) and transplantation > 1 year from diagnosis (RR = 1.68; $P = .002$) were associated with higher risk of NRM. Pre-transplant rituximab did not affect NRM ($P = .18$) (Table 2). Causes of death were similar in the +R and −R cohorts, with 58%-60% of deaths from lymphoma and

40%-42% of deaths from causes other than relapse (Table 3).

Relapse/progression and PFS

The risk of relapse/progression was lower in the +R cohort compared with the −R cohort (RR = 0.67; P = .004). Other significant covariates associated with higher risk of relapse/progression were older age (≥ 55 years; RR=1.36; $P = .002$), lack of a CR or chemosensitive status at transplantation ($P < .001$), and 3 or more lines of previous chemotherapy (RR = 1.71; $P < .001$).

PFS was superior in the +R cohort, resulting in a lower risk of treatment failure from relapse/progression or death in this cohort (RR = 0.64; $P < .001$) (Table 4; Figure 3). Pointwise estimates of PFS at the 1- and 3-year time points for the +R and −R cohorts were 62% versus 49% ($P = .002$) and 50% versus 38% ($P = .008$), respectively. Other significant covariates associated with improved PFS and lower risk of treatment failure were age < 55 years, first CR at the time of transplantation, and fewer than 3 lines of previous chemotherapy (Table 4).

OS

OS was superior in the +R cohort, with a lower risk of mortality (RR = 0.74; $P = .039$) (Table 5; Figure 4). Pointwise estimates of OS at the 1- and 3-year time points for the +R and −R cohorts were 68% versus 60% ($P = .049$) and 57% versus 45% ($P = .006$), respectively. In multivariate analysis, age < 55 years, first CR at the time of transplantation, fewer than 3 lines of chemotherapy, and later year of transplantation were all associated with lower mortality and improved survival (Table 5).

Timing of rituximab

The average interval from last rituximab dose to transplantation was 5 months. Analysis revealed no significant differences in PFS (Figure 5A) or OS (Figure 5B) between patients receiving rituximab within 6 months of transplantation and those receiving rituximab > 6 months before transplantation.

DISCUSSION

The Parma trial remains the only published prospective, randomized trial comparing salvage chemotherapy alone with AuHCT for relapsed DLBCL. Based on that study, AuHCT has remained the standard of care for patients with chemosensitive relapsed and refractory DLBCL [6]. The Parma trial predates the introduction of rituximab into clinical practice; in contrast, patients with DLBCL are now routinely treated with rituximab as part of front-line and/or subsequent therapy. As a result, the outcomes after AuHCT for DLBCL in the rituximab era are not fully known. Our results indicate that pre-transplant rituximab is not associated with impaired engraftment or increased NRM. In addition, improved PFS and OS were seen in the +R cohort.

There are several possible explanations for our observation of enhanced PFS and OS after AuHCT in the +R cohort:

1. It is possible that the +R cohort was a more favorable group based on baseline patient characteristics. However, this seems unlikely because these patients were actually older than those in the –R cohort. Moreover, the 2 cohorts were very similar in terms of IPI score at transplantation, disease status at transplantation, performance status, stage, chemosensitivity, and bulky disease.
2. The fact that the +R cohort underwent transplantation in later years than the −R cohort also might account for the better outomes in the +R cohort. However, this would be expected to influence

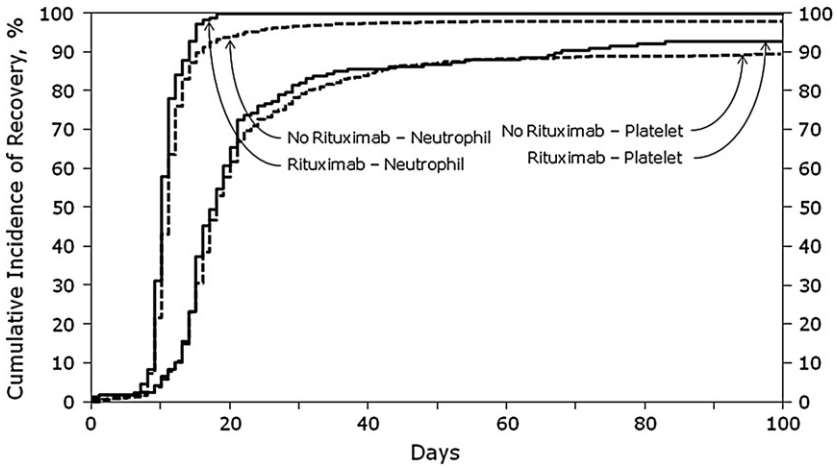

Figure 1. Cumulative incidence of neutrophil and platelet recovery after AuHCT for DLBCL analyzed by whether or not rituximab was given before transplantation.

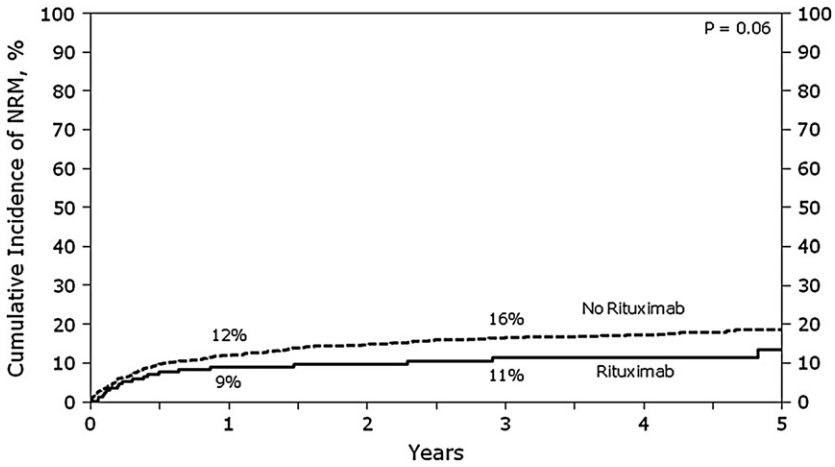

Figure 2. Cumulative incidence of NRM after AuHCT for DLBCL analyzed by whether or not rituximab was given before transplantation.

survival only by decreasing NRM (because of improvements in supportive care over time), and would not be expected to affect PFS (because both cohorts received similar conditioning regimens). There was no significant difference in NRM between the 2 cohorts.

3. In theory, the better PFS and OS in the +R cohort could result from the delayed activity of rituximab received during salvage therapy. However, the average interval from the last rituximab dose to transplantation was 5 months, and no significant differences in 1-, 3-, or 5-year PFS or OS were seen between patients receiving rituximab within 6 months of transplantation and those receiving rituximab > 6 months before transplantation.
4. Pre-transplant rituximab might possibly sensitize or alter specific effector cell populations, or affect immune reconstitution in ways that lead to enhanced anti-lymphoma effects. Unfortunately, posttransplant immune reconstitution data were not uniformly collected from the patients in this study, precluding further testing of this hypothesis.
5. Finally, it is known that inclusion of rituximab in first-line therapy has improved the outcome of specific subsets of DLBCL, such as those which are *bcl6*-negative, *bcl2*-positive, or of nongerminal center origin [10-12]. As a result, there could be important biological differences between our +R and −R cohorts that might account for the improved outcome of the +R cohort after AuHCT.

Table 2. Multivariate Analyses for NRM*

Variables	n	RR of NRM (95% CI)	*P* Value
Main effect			
No rituximab	812	1.00	
Rituximab	174	0.70 (0.41-1.18)	.18
Other significant covariates			
Age at transplantation, years			
<55	562	1.00	
≥ 55	424	1.79 (1.31-2.45)	< .001
Time from diagnosis to transplantation, years			
≤1	435	1.00	
>1	551	1.68 (1.21-2.34)	.002
Year of transplantation			
1996-1999	728	1.00	
2000-2003	258	0.63 (0.40-1.00)	.05

NRM indicates nonrelapse mortality.
*Cox models stratified on Karnofsky performance score.

Although several cases of delayed neutropenia associated with rituximab have been described [13,14], the stem cell yield after rituximab therapy appears to be unaffected [7,15]. An additional concern is that pre-transplantation rituximab may affect engraftment kinetics [7]. Our findings support the concept that pre-transplant exposure to rituximab does not compromise peripheral blood stem cell (PBSC) product quality or engraftment.

One might expect *a priori* that patients with relapsed or refractory DLBCL already exposed to rituximab will be more likely to have rituximab-refractory disease, and thus also will be inherently more difficult to rescue with rituximab-containing salvage therapy followed by AuHCT. But, our data appear to contradict this notion; those patients previously exposed to rituximab actually had improved PFS and OS.

It is possible that the outcomes after AuHCT may differ, depending on the exact timing of exposure to

Table 3. Causes of Death before Day 100

	+R Cohort		-R Cohort	
Cause of death	n Evaluable	n (%)	n Evaluable	n (%)
Number of patients	24		114	
Relapse/progression		14 (58)		68 (60)
Other causes		10 (42)		46 (40)
Pulmonary syndrome		2 (8)		10 (9)
Infection		2 (8)		11 (9)
Organ failure		3 (14)		19 (17)
Hemorrhage		1 (4)		4 (3)
New malignancy		1 (4)		1 (1)
Unknown		1 (4)		1 (1)

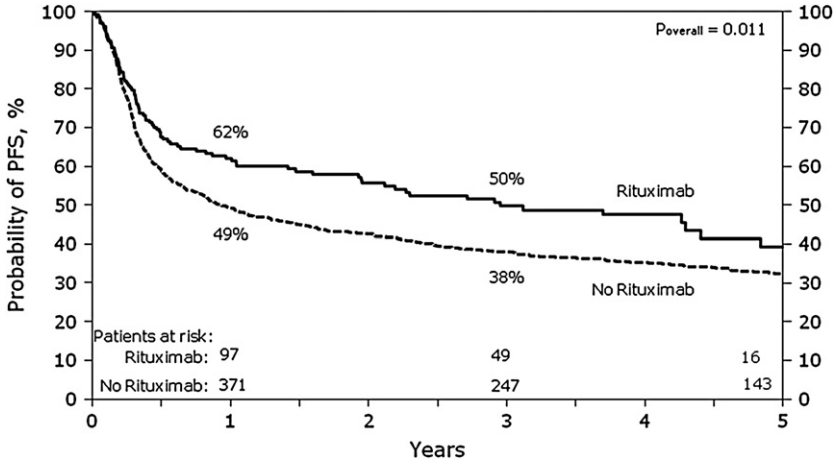

Figure 3. Probability of PFS after AuHCT for DLBCL analyzed by whether or not rituximab was given before transplantation.

rituximab (as part of first-line therapy and/or salvage therapy). The number of patients in the +R cohort was not sufficient to allow for meaningful subgroup analysis based on rituximab exposure during first-line therapy or salvage therapy, so our study does not shed light on this issue. In a recently published study from the Gruppo Italiano Terapie Innnovative nei Linfomi, the benefit of rituximab before AuHCT was most apparent in the patients with follicular lymphoma and DLBCL who received rituximab with salvage therapy but not with first-line therapy [16]. In a much smaller study from Germany, an improved outcome after AuHCT for aggressive NHL was associated with the addition of rituximab to salvage therapy. In that study, patients were largely (87%) rituximab-naïve before salvage therapy [17]. Ashraf et al. [18] recently reported single-center outcomes of 63 patients with DLBCL who underwent AuHCT between 1991 and 2008. Similar to our findings, significantly better disease control after AuHCT was seen in the patients who received rituximab as part of front-line therapy. In the ongoing CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) Study, relapsed and refractory CD20-positive DLBCL patients are randomized between 2 different rituximab-based salvage chemotherapy regimens, followed by AuHCT and then a second randomization of observation versus maintenance rituximab [19]. The CORAL Study enrolls both patients with and without rituximab in first-line therapy and on

Table 4. Multivariate Analysis for PFS*

Variables	n	RR of Relapse/ Progression or Death (95% CI)	*P* Value
Main effect			
No rituximab	812	1.00	
Rituximab	174	0.64 (0.50-0.81)	< .001
Other significant covariates			
Age at transplantation, years			
< 55	562	1.00	
≥ 55	424	1.45 (1.23-1.71)	< .001
Disease status at transplantation			
CR1	167	1.00	< .001†
PIF-sensitive	182	1.24 (0.91-1.69)	.18
PIF-resistant	54	3.38 (2.30-4.96)	< .001
Relapse-sensitive	298	2.02 (1.53-2.67)	< .001
Relapse-resistant	69	2.65 (1.83-3.82)	< .001
CR2+	158	1.57 (1.14-2.14)	.010
Unknown	58	2.13 (1.45-3.15)	.001
Number of lines of chemotherapy			
≤ 2	561	1.00	< .001‡
> 2	418	1.61 (1.36-1.91)	< .001

PFS indicates progression-free survival; RR, relative risk; PIF, pulmonary induction failure; CR, complete remission.
*Cox models stratified on Karnofsky performance score.
†Six degrees of freedom.
‡Two degrees of freedom.

Table 5. Multivariate Analysis for OS*

Variable	n	RR of Death (95% CI)	*P* Value
Main effect			
No rituximab	818	1.00	
Rituximab	176	0.74 (0.56-0.99)	.039
Other significant covariates			
Age at transplantation, years			
< 55	568	1.00	
≥ 55	426	1.53 (1.29-1.83)	< .001
Disease status at transplantation			
CR1	168	1.00	< .001†
PIF-sensitive	184	1.29 (0.91-1.82)	.15
PIF-resistant	54	3.23 (2.14-4.87)	< .001
Relapse-sensitive	301	2.06 (1.51-2.81)	< .001
Reapse-resistant	69	2.57 (1.73-3.83)	< .001
CR2+	159	1.58 (1.12-2.24)	.010
Unknown	59	2.27 (1.50-3.44)	< .001
Number of lines of chemotherapy			
≤ 2	564	1.00	< .001‡
> 2	422	1.53 (1.28-1.82)	< .001
Year of transplantation			
1996-1999	735	1.00	
2000-2003	259	0.73 (0.57-0.94)	.013

OS indicates overall survival; RR, relative risk; PIF, pulmonary induction failure; CR, complete remission.
*Cox models stratified on Karnofsky performance score.
†Six degrees of freedom.
‡Two degrees of freedom.

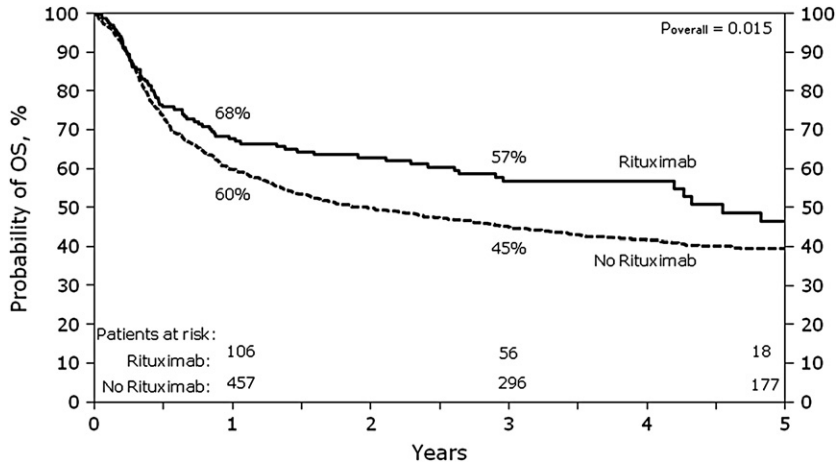

Figure 4. Probability of OS after AuHCT for DLBCL analyzed by whether or not rituximab was given before transplantation.

completion hopefully will further clarify the impact of rituximab exposure at different time points before transplantation.

The patient cohorts in the present study are representative of a period of transition in practice when the use of rituximab was increasingly being used to treat DLBCL. Thus, a contemporary cohort of patients who were rituximab-naïve at the time of AuHCT was available for comparison with the +R cohort. In the context of current clinical practice in the United States, rituximab is generally used in both first-line and subsequent therapies for DLBCL; thus, it is highly unlikely

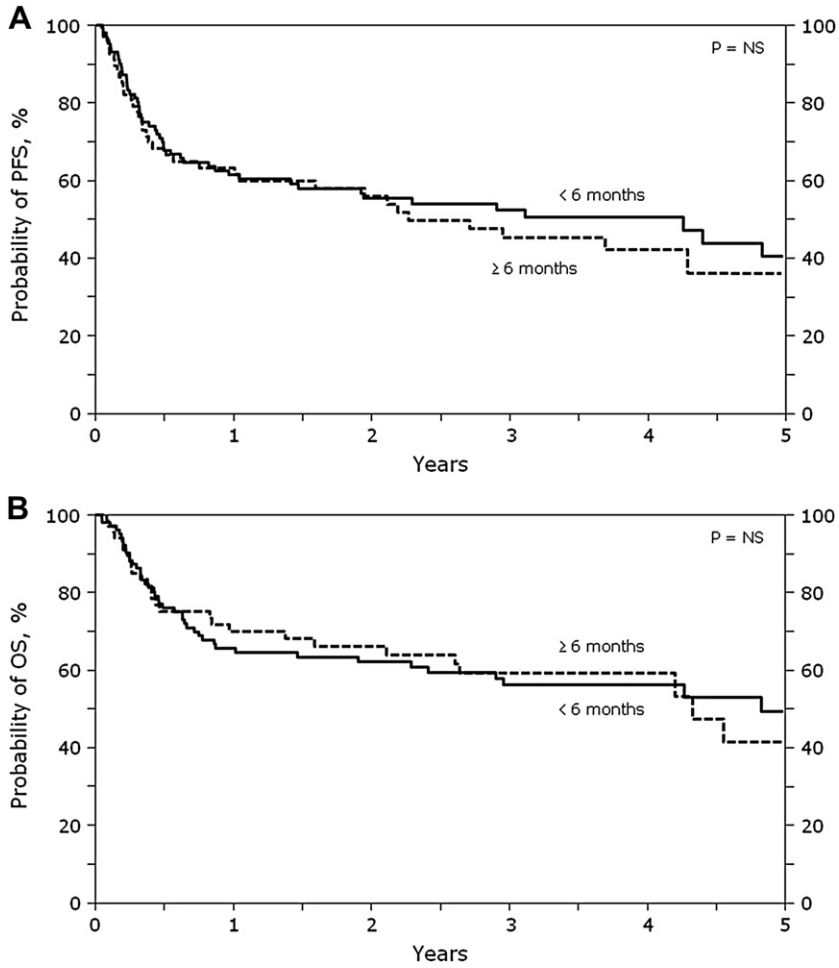

Figure 5. A, Probability of PFS after AuHCT for DLBCL analyzed by whether or not rituximab was given < 6 months or ≥ 6 months before transplantation. B, Probability of OS after AuHCT for DLBCL analyzed by whether rituximab was given < 6 months or ≥ 6 months before transplantation.

that current AuHCT recipients for DLBCL will be rituximab-naive. Nonetheless, our findings provide *post hoc* validation for this practice and confirm the safety of previous rituximab therapy in the AuHCT setting.

In this study, with a median of 42 months of follow-up in the +R cohort, there were only a small number of patients with 5 or more years of follow-up. Thus, it was not possible to perform statistically significant analyses of longer-term survival outcomes beyond those reported here. The magnitude of the benefit of pretransplant rituximab beyond 5 years after AuHCT remains uncertain. Longer follow-up would help clarify whether rituximab only serves to delay DLBCL relapse or whether it leads to a higher rate of long-term disease-free survival. The question of whether post-AuHCT "maintenance" therapy (using rituximab and/or other agents) may offer a benefit for patients with DLBCL also remains unanswered. Long-term data from randomized trials, such as the ongoing CORAL Study, are needed to further address these questions.

ACKNOWLEDGMENTS

Financial disclosure: The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID); Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; Contract HHSH234200637015C from the Health Resources and Services Administration; Grants N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from AABB; Aetna; American Society for Blood and Marrow Transplantation; Amgen, Inc; anonymous donation to the Medical College of Wisconsin; Association of Medical Microbiology and Infectious Disease Canada; Astellas Pharma US, Inc; Baxter International, Inc; Bayer HealthCare Pharmaceuticals; BloodCenter of Wisconsin; Blue Cross and Blue Shield Association; Bone Marrow Foundation; Canadian Blood and Marrow Transplant Group; Celgene Corp; CellGenix GmbH; Centers for Disease Control and Prevention; ClinImmune Labs; CTI Clinical Trial and Consulting Services; Cubist Pharmaceuticals; Cylex, Inc; CytoTherm; DOR BioPharma, Inc; Dynal Biotech, an Invitrogen Company; Enzon Pharmaceuticals, Inc; European Group for Blood and Marrow Transplantation; Gambro BCT, Inc; Gamida Cell, Ltd; Genzyme Corp; Histogenetics, Inc; HKS Medical Information Systems; Hospira, Inc; Infectious Diseases Society of America; Kiadis Pharma; Kirin Brewery Co, Ltd; Merck & Company; Medical College of Wisconsin; MGI Pharma, Inc; Michigan Community Blood Centers; Millennium Pharmaceuticals, Inc; Miller Pharmacal Group; Milliman USA, Inc; Miltenyi Biotec, Inc; National Marrow Donor Program; Nature Publishing Group; New York Blood Center; Novartis Oncology; Oncology Nursing Society; Osiris Therapeutics, Inc; Otsuka Pharmaceutical Development & Commercialization, Inc; Pall Life Sciences; PDL BioPharma, Inc; Pfizer Inc; Pharmion Corp; Saladax Biomedical, Inc; Schering Plough Corp; Society for Healthcare Epidemiology of America; StemCyte, Inc; StemSoft Software, Inc; Sysmex; Teva Pharmaceutical Industries; The Marrow Foundation; THERAKOS, Inc; Vidacare Corp; Vion Pharmaceuticals, Inc; ViraCor Laboratories; ViroPharma, Inc; and Wellpoint, Inc.

The views expressed in this article do not reflect the official policy or position of the national institutes of health (NIH), the Department of the Navy, the Department of Defense, or any other agency of the U.S. Government.

REFERENCES

1. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993;329:987-994.
2. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379-391.
3. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23:4117-4126.
4. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol*. 2005;23:5027-5033.
5. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 2007;109:1857-1861.
6. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333:1540-1545.
7. Hoerr AL, Gao F, Hidalgo J, et al. Effects of pre-transplant treatment with rituximab on outcomes of autologous stem-cell transplantation for non-Hodgkin's lymphoma. *J Clin Oncol*. 2004;22:4561-4566.
8. Klein JP, Moeschberger ML. *Survival Analysis: Techniques For Censored And Truncated Data*. New York: Springer; 2003.
9. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc*. 1958;53.
10. Mounier N, Briere J, Gisselbrecht C, et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2–associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). *Blood*. 2003;101:4279-4284.
11. Winter JN, Weller EA, Horning SJ, et al. Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP: a prospective correlative study. *Blood*. 2006;107:4207-4213.
12. Nyman H, Adde M, Karjalainen-Lindsberg ML, et al. Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Blood*. 2007;109:4930-4935.

13. Chaiwatanatorn K, Lee N, Grigg A, et al. Delayed-onset neutropenia associated with rituximab therapy. *Br J Haematol*. 2003; 121:913-918.
14. Motl SE, Baskin RC. Delayed-onset grade 4 neutropenia associated with rituximab therapy in a patient with lymphoma: case report and literature review. *Pharmacotherapy*. 2005;25:1151-1155.
15. Benekli M, Hahn T, Shafi F, et al. Effect of rituximab on peripheral blood stem cell mobilization and engraftment kinetics in non-Hodgkin's lymphoma patients. *Bone Marrow Transplant*. 2003;32:139-143.
16. Tarella C, Zanni M, Magni M, et al. Rituximab improves the efficacy of high-dose chemotherapy with autograft for high-risk follicular and diffuse large B-cell lymphoma: a multicenter Gruppo Italiano Terapie Innnovative nei linfomi survey. *J Clin Oncol*. 2008;26:3166-3175.
17. Sieniawski M, Staak O, Glossmann JP, et al. Rituximab added to an intensified salvage chemotherapy program followed by autologous stem cell transplantation improved the outcome in relapsed and refractory aggressive non-Hodgkin lymphoma. *Ann Hematol*. 2007;86:107-115.
18. Ashraf U, Mahajan R, Hahn R, et al. The effects of rituximab added to front-line or salvage chemotherapy in diffuse large B-cell lymphoma (DLBCL) undergoing high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT). *Blood*. 2008;112. abstract 1138.
19. Gisselbrecht C, Schmitz N, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by stem cell transplantation and maintenance treatment with rituximab or not: First interim analysis on 200 patients. CORAL Study. *Blood*. 2007;110. abstract 517.