Regular Article

TRANSPLANTATION

Rituximab prophylaxis prevents corticosteroid-requiring chronic GVHD after allogeneic peripheral blood stem cell transplantation: results of a phase 2 trial

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Key Points

- Rituximab prevents steroid-requiring chronic graft-vs-host disease when given after peripheral blood stem cell transplantation.
- Overall survival is improved with rituximab after allogeneic peripheral blood stem cell transplantation when compared with a control cohort.

B cells are implicated in the pathophysiology of chronic graft-vs-host disease (GVHD), and phase 2 trials suggest that B cell depletion can treat established chronic GVHD. We hypothesized that posttransplantation B cell depletion could prevent the occurrence of chronic GVHD. We performed a 65-patient phase 2 trial of rituximab (375 mg/m^2 IV), administered at 3, 6, 9, and 12 months after transplantation. Rituximab administration was safe without severe infusional adverse events. The cumulative incidences of chronic GVHD and systemic corticosteroid-requiring chronic GVHD at 2 years from transplantation were 48% and 31%, respectively, both lower than the corresponding rates in a concurrent control cohort (60%, $P = .1$, and 48.5%, $P = .015$). There was no difference in relapse incidence, but treatment-related mortality at 4 years from transplantation was significantly lower in treated subjects when compared with controls (5% vs 19%, $P = .02$), and overall survival was superior at 4 years (71% vs 56%, $P = .05$). At 2 years from transplantation, the B-cell activating factor/B-cell ratio was significantly higher in subjects who developed chronic GVHD in comparison with those without chronic GVHD ($P = .039$).

Rituximab can prevent systemic corticosteroid-requiring chronic GVHD after peripheral blood stem cell transplantation and should be tested in a prospective randomized trial. This trial was registered at www.clinicaltrials.gov as NCT00379587. (*Blood*. 2013;122(8):1510-1517)

Introduction

Chronic graft-versus-host disease (GVHD) is the leading cause of late morbidity, impaired quality of life, and mortality after allogeneic stem cell transplantation.[1-3] Efforts to pharmacologically prevent chronic GVHD by extending the period of immunosuppression after allogeneic transplantation have not been successful.[4,5] The use of T-cell depletion, either with in vivo (polyclonal or monoclonal antibody therapy)[6-8] or ex vivo (T-cell depletion or CD34$^+$ selection)[9] methodologies has been shown to prevent chronic GVHD; however, this has not been associated with an improvement in overall survival because of excess mortality associated with opportunistic infections and possibly malignant disease relapse. Finally, allogeneic tolerance induction with the use of posttransplantation cyclophosphamide has been shown to prevent chronic GVHD, but long-term outcomes have not been compared with traditional GVHD prevention strategies.[10]

Because prolongation of calcineurin inhibition after transplantation does not prevent the occurrence of chronic GVHD, alternative, non-T-cell–dependent pathways that can lead to alloreactivity can be implicated in the pathogenesis of chronic GVHD in some patients. B-cell-dependent processes have thus been implicated following

several lines of evidence: antibodies against minor histocompatibility antigens have been associated with the occurrence of chronic GVHD[11]; B-cell depletion in the peritransplantation period has been correlated with a reduction in chronic GVHD incidence[12]; and most important, B-cell–depletion therapy with rituximab is effective in the therapy of established chronic GVHD.[13-19] In addition, murine models of chronic GVHD and bronchiolitis obliterans have implicated donor B-cell alloantibodies in the pathogenesis of this disease.[20]

Much work has focused on the potential role of B cells in pathobiology of chronic GVHD. It is known that B-cell reconstitution in patients with chronic GVHD is delayed, and these patients have elevated plasma B-cell activating factor (BAFF) to B-cell ratios.[21] Altered B-cell homeostasis in chronic GVHD is associated with persistence of circulating, potentially autoreactive, B cells.[21,22] Further supporting a mechanistic role for B cells in human chronic GVHD are studies demonstrating altered signaling through the BAFF-associated and B-cell-receptor–associated pathways.[23,24]

Recently, in a small series of patients with aggressive B-cell malignancies treated with rituximab in the early posttransplantation

period, a reduction in the rate of chronic GVHD was noted[25]; however, patients were treated using a preparative regimen that traditionally is associated with low rates of chronic GVHD.[26] Because chronic GVHD occurs more frequently after peripheral blood stem cell transplantation,[27,28] we conducted a phase 2 trial of rituximab given specifically for the prevention of chronic GVHD after allogeneic peripheral blood stem cell transplantation.

Methods

This was a prospective, open-label, phase 2 trial of prophylactic rituximab given to prevent the occurrence of chronic GVHD after allogeneic stem cell transplantation. The clinical trial was approved by the Office for Human Research Studies at the Dana-Farber Cancer Institute/Harvard Cancer Center and was registered at www.clinicaltrials.gov (NCT00379587). Genentech (San Francisco, CA) provided rituximab for all enrolled subjects. Informed consent was obtained in accordance with the Declaration of Helsinki.

The primary objectives of the trial were to determine the incidence of chronic GVHD and corticosteroid-requiring chronic GVHD at 1 and 2 years after allogeneic stem cell transplantation. Corticosteroid-requiring chronic GVHD was added as an end point after the completion of the trial, but before data analysis. Secondary objectives were to determine the incidence of hematological and nonhematological adverse events when rituximab was administered in the posttransplantation setting. Eligible patients were 18 years of age or greater and received a nonmyeloablative or myeloablative transplantation using peripheral blood stem cells from an 8/8 HLA-matched donor or single antigen/allele-mismatched donor approximately 100 days prior to enrollment. Adequate performance status and organ function was required, and subjects were free of uncontrolled infection and active acute GVHD at the time of enrollment. Prior resolved acute GVHD was permitted. Subjects were required to have evidence of sustained donor chimerism and underwent disease restaging to exclude relapse at the time of enrollment. Subjects participating in clinical trials of primary GVHD prophylaxis in which chronic GVHD was a secondary end point were not enrolled. Any subject with evidence of classic chronic GVHD or overlap chronic GVHD was ineligible to participate, as was any subject who had previously received donor lymphocyte infusions to treat relapse or falling donor chimerism.

Rituximab (375 mg/m^2 IV) was administered at 100 days, and again at 6, 9, and 12 months after transplantation. Premedication with H$_1$- and H$_2$-blockers and acetaminophen was provided. Corticosteroids were not used as premedication. Systemic immunosuppressive medications were tapered at the treating clinician's discretion per institutional standards. Upon the occurrence of chronic GVHD, initial and subsequent immunosuppressive treatment was administered according to institutional standards as well.

Correlative studies for B-cell reconstitution and BAFF levels

A commercially available sandwich enzyme-linked immunosorbent assay (ELISA) was used in order to measure soluble BAFF/Blys levels from patient plasma (R&D Systems, Minneapolis, MN). Whole blood or viable frozen ficolled peripheral blood mononuclear cells were processed for flow cytometry. Lymphocytes were gated by size using forward and side scatter criteria. A total of 50 000 lymphocytes were collected for all samples to ensure adequate total numbers of B cells for subset analysis. Anti-CD19 PC7 (Beckman Coulter, Brea, CA) was used per manufacturer's instructions. CD19 expression was analyzed to exclude CD3$^+$ cells from the analysis of CD38 or CD27 expression. Red blood cells (RBCs) were lysed, and leukocytes were fixed prior to fluorescence-activated cell sorter (FACS). A MACSQuant Analyzer (Miltenyi Biotech, Auburn, CA) was used, and data were analyzed using FlowJo software (Tree Star, Ashland, OR).

Statistical design and analysis

transplantation, this study was designed to accrue these 2 cohorts separately but in parallel, with the null hypothesis of a rate of chronic GVHD of 45% after matched, related transplantation and 65% after matched, unrelated transplantation. The alternative hypothesis was a 20% reduction with the use of rituximab in both cohorts. With this hypothesis, using an exact binomial distribution, the probability of concluding rituximab promising was 0.88 if the true but unknown rate of developing chronic GVHD is 25% and 0.09 if the true rate is 45% in matched, related donor transplantation and 0.86 if the true but unknown rate of developing chronic GVHD is 45% and 0.10 if the true rate is 65% in matched, unrelated transplantation. These statistical parameters do not apply to the estimates of corticosteroid-requiring chronic GVHD.

Although not part of the original statistical design, a contemporaneous control cohort was constructed from our database using patients treated during the same time interval who chose not to participate in this trial. Control patients were selected randomly from the database using the identical selection criteria as for the clinical trial population. A similar proportion of recipients of matched, related and unrelated donors as accrued in the prospective trial was purposefully chosen for comparison.

Baseline characteristics were reported descriptively, and compared using the χ^2 test, Fisher's exact test, or Wilcoxon rank-sum test. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. OS was defined as the time from stem cell infusion to death from any cause. Patients who were alive or lost to follow-up were censored at the time last seen alive. PFS was defined as the time from stem cell infusion to disease relapse or progression or death from any cause, whichever occurred first. Patients who were alive without disease relapse or progression were censored at the time last seen alive and progression-free. The log-rank test was used for comparisons of Kaplan-Meier curves. The cumulative incidence of grade 3 or higher infections was calculated considering death unrelated to infections and relapse as competing events. Cumulative incidences of chronic GVHD and systemic corticosteroid-requiring chronic GVHD were calculated using competing risks reflecting time to relapse or death without developing chronic GVHD or corticosteroid-requiring chronic GVHD as competing events. Late acute GVHD was not considered to be chronic GVHD unless overlap features were present. Similarly, cumulative incidences of nonrelapse death and relapse with or without death were calculated using competing risks, reflecting time to relapse and time to nonrelapse death, respectively, as competing risks. The difference between cumulative incidence curves in the presence of a competing risk was tested using the Gray method.[29] Potential prognostic factors for OS, PFS, and corticosteroid-requiring chronic GVHD were examined in the proportional hazards model as well as in the competing risks regression model.[30] Factors included in the multivariable models were age, patient–donor sex mismatch, myeloid disease (Y/N), donor type, conditioning intensity, disease relapse index,[31] and grades II-IV acute GVHD. The occurrence of grade II-IV acute GVHD was treated as a time-dependent variable in multivariable analysis. The proportional hazards assumption was tested, and interaction terms were examined. All tests are 2-sided at a significance level of 0.05. All calculations were done using SAS 9.3 (SAS Institute, Inc., Cary, NC) and R version 2.13.2 (the Comprehensive R Archive Network [CRAN] project [http://cran.us.r-project.org/]).

Results

Between December 2006 and October 2010, 65 subjects were enrolled and treated on this clinical trial. The data set was locked and analyzed in March 2012, when all subjects had at least 2 years of posttransplantation follow-up, with a median follow-up of 48 months.

The median age of enrolled subjects was 54 years, and 31 subjects received peripheral blood stem cell grafts from matched, related donors. One subject received a 7/8 unrelated donor transplant

Table 1. Baseline clinical characteristics

	Rituximab-treated subjects (n = 65)		Controls (n = 68)		
	N	%	N	%	P value
Age, median (range)	54 (19-74)		54 (26-70)		.81
Gender					1.00
M	39	60	41	60.3	
F	26	40	27	39.7	
Donor gender					1.00
M	38	58.5	39	57.4	
F	27	41.5	29	42.6	
Subject–donor gender					.87
FF	9	13.8	12	17.6	
FM	17	26.2	15	22.1	
MF	18	27.7	17	25	
MM	21	32.3	24	35.3	
Diagnosis					.57
AML	30	46.2	31	45.6	
CLL/SLL/PLL	2	3.1	3	4.4	
HD	1	1.5	1	1.5	
ALL	4	6.2	5	7.4	
MDS	6	11.1	7	10.3	
MPD	4	6.2			
Mixed MDS/MPD			1	1.5	
NHL	18	27.7	20	29.4	
Disease relapse index					.49
Low	10	15.4	10	14.7	
Intermediate	38	58.5	32	47.1	
High	15	23.1	22	32.4	
Very high	2	3.1	4	5.9	
Disease status at transplantation					
Active	30	46.1	28	41.2	.60
Remission	35	53.8	40	58.8	
Donor type					
8/8 MRD	31	47.7	30	44.1	.52
8/8 MUD	33	50.8	38	55.9	
7/8 mismatched unrelated	1	1.5			
Conditioning intensity					
MAC	25	38.5	28	41.2	.86
RIC	40	61.5	40	58.8	
Stem cell source					
PBSC	65	100	68	100	1.00
GVHD prophylaxis regimen					
CI$^{+/-}$ Mtx$^{+/-}$ other	22	33.8	26	38.2	.72
CI$^{+/-}$ Siro$^{+/-}$ other	43	66.2	42	61.8	
Grade II-IV acute GVHD	9	13.8	12	17.6	.64
Grade III-IV acute GVHD	2	3.1	5	7.4	.44
Corticosteroid use at rituximab initiation/day 100	5	7.7	9	13.2	.57
Corticosteroid dose (mg/kg) at rituximab initiation/ day 100 (median, range)	0.13	(0.06-0.38)	0.34	(0.11-0.93)	.09

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, calcineurin inhibitor; CLL/SLL/PLL, chronic lymphocytic leukemia/small lymphocytic lymphoma/prolymphocytic Leukemia; F, Female; HD, Hodgkin Disease; M, Male; MAC, myeloablative conditioning; MDS, myelodysplastic disorder; MPD, myeloproliferative disease; MRD, matched, related donor; Mtx, methotrexate; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning.

reduced-intensity conditioning, and acute leukemia was the most common diagnosis (52.3%), with advanced B-cell malignancies accounting for 32.3% of enrolled subjects. All subjects received peripheral blood stem cells, but only 13.8% had grades II-IV acute GVHD. Only 2 subjects received anti-thymocyte globulin as part of their conditioning regimen (Table 1).

Safety and adverse events

4 doses included the development of chronic GVHD (18), relapse (13), and patient preference (2). Thirty-two subjects completed all 4 doses of rituximab, including some individuals who had developed chronic GVHD during the first year after transplantation.

There were no grades 3-4 events associated with rituximab infusion. There were 2 reports of grades 3-4 thrombocytopenia considered possibly or probably related to therapy with rituximab. Leukopenia or neutropenia considered possibly or probably related to therapy with rituximab was reported in 9 subjects and was

Table 2. Toxicities and attribution to rituximab

		Grade		
Relation to rituximab	Toxicity	3	4	5
Possible	Transaminitis	2		
	Hemolysis	1		
	Leukopenia/neutropenia	4		
	Thrombocytopenia	1		
Probable	Constipation	1		
	Anemia	1		
	Leukopenia/neutropenia	1	3	
	Thrombocytopenia		1	
	Alkaline phosphatase elevation	1		
Definite	Flu-like syndrome	1		
	Leukopenia/neutropenia	1		

an adverse event, and subjects were permitted to receive replacement therapy outside of the transplantation center. Ten patients experienced 15 episodes of grade 3 or higher infections. The 1- and 2-year cumulative incidence of grade 3 or higher infections was 11% and 15%, respectively. There were 2 lethal infections, with 1 being considered possibly related to rituximab.

Incidence of chronic GHVD

The cumulative incidence of clinician-diagnosed chronic GVHD at 1 and 2 years after transplantation was 38% and 48%, respectively. The corresponding figures for related and unrelated donor recipients were 29% and 35% for related donors, and 47% and 59% for unrelated donors, which were significantly different ($P = .046$) (Figure 1A-B).

We measured the requirement of initiation of systemic corticosteroids as a surrogate for chronic GVHD severity. The cumulative incidence of systemic corticosteroid-requiring chronic GVHD was only 21.5% and 31% at 1 and 2 years from transplantation, respectively. The corresponding figures at 1 and 2 years were 16% and 23% for related donors, and 26% and 38% for unrelated donors ($P = .17$) (Figure 1A-B). At 1 year from transplantation, 19 subjects (5 related donors, 14 unrelated donors) were using systemic corticosteroids, and 47.7% of subjects were using some form of systemic immunosuppression (38.7% related donors, 55.9% unrelated donors).

Mucosal chronic GVHD, with ocular and oral involvement, was the most common manifestation of chronic GVHD (24.5% and 22.6% of subjects, respectively). Because there was much less systemic corticosteroid use in these patients, it appeared that mucosal GVHD was not considered severe enough to warrant corticosteroids. Notably, both cutaneous and myofascial disease, which have previously been reported to be responsive to rituximab therapy,[13] was noted only in 13.2% and 5.7% of subjects, respectively.

Immunophenotypic correlations

B-cell lymphopenia was profound, and B cells were unmeasurable during the year following rituximab administration in almost all treated subjects. At 18 months from transplantation (6 months following the final rituximab administration), B cells remained essentially absent, but by 24 months from transplantation, B-cell reconstitution was noted. At 24 months from transplantation, the median number of B cells in treated patients who did not develop chronic GVHD was 138.5 cells/μL in comparison with only 9.9 cells/μL in treated patients with chronic GVHD ($P = .047$)

entry, and at months 4 and 6 following transplantation (1 and 3 months following initial rituximab administration). BAFF levels were significantly higher in chronic GVHD-free patients at 9 and 12 months from transplantation (17.7 ng/mL vs 11.2 ng/mL, $P = .033$; 16.7 ng/mL vs 8.1 ng/mL, $P < .01$, respectively); however, there was no difference at 18 and at 24 months, at which point B cells had reconstituted (Figure 2). Consistent with prior observations,[21] the BAFF/B-cell ratio was significantly higher in chronic GVHD patients than in chronic GVHD-free patients at 24 months ($P = .039$).

Relapse and survival

The median follow-up among surviving patients was 48 months (range, 26 to 77 months). The 4-year cumulative incidence of relapse was 34%. There was no difference in relapse between CD20$^+$ malignancies and CD20$^-$ malignancies in rituximab-treated subjects (32% vs 36%). Nonrelapse mortality, an additional surrogate of chronic GVHD severity, was very low, with only 2 subjects dying of nonrelapse-related causes at 2 years from transplantation with a cumulative incidence of 5.1% at 4 years from transplantation. The 4-year estimates of PFS and OS were 61% and 71%, respectively.

Comparison with control cohort

After completion of the trial, a contemporaneous control cohort was constructed from our database using patients treated during the same time interval who chose not to participate in this trial. Baseline clinical characteristics of the control cohort can be found in Table 1.
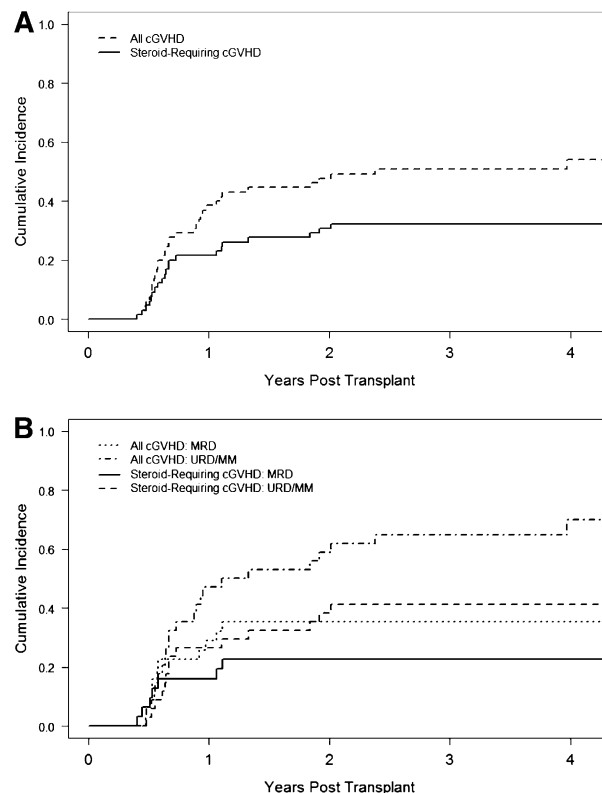

Figure 1. Chronic GVHD incidence. (A) Overall incidence of chronic GVHD. Dashed line, incidence of all chronic GVHD; solid line, incidence of corticosteroid-requiring chronic GVHD. (B) Incidence of chronic GVHD stratified by donor type. Dotted line, incidence of all chronic GVHD, matched related donors; solid line, incidence of corticosteroid-requiring chronic GVHD, matched related donors; dot-
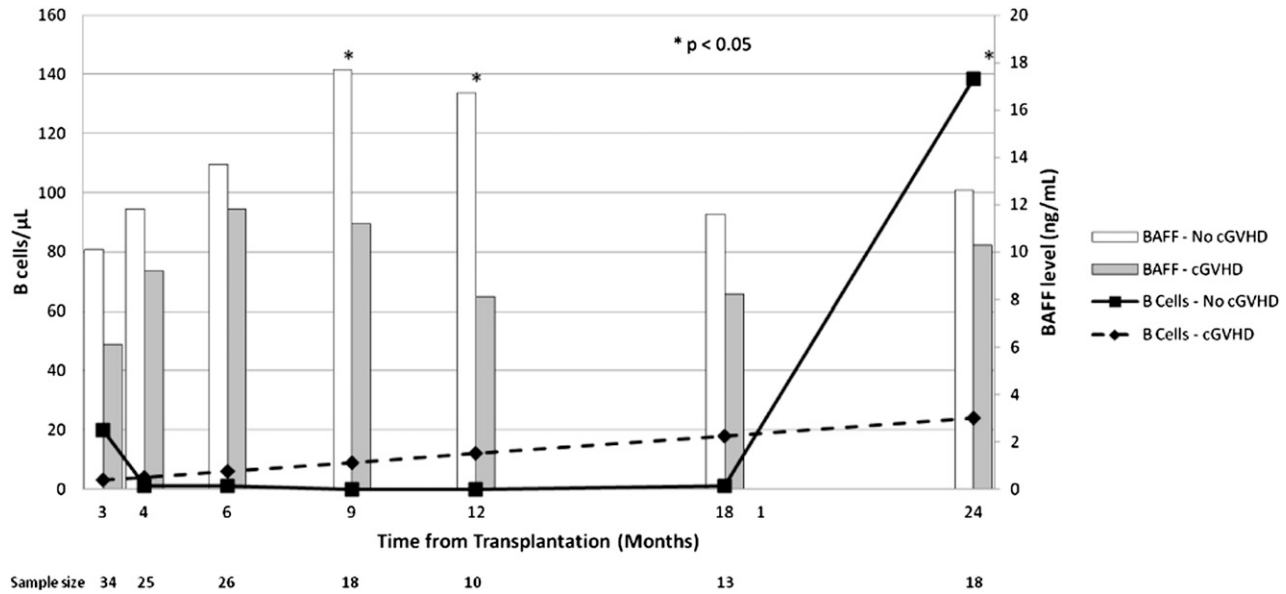
Figure 2. Immunophenotypic outcomes. Bar graph shows median BAFF levels. Open bar, no chronic GVHD; shaded bar, chronic GVHD. Line graph shows median B-cell numbers. Dashed line, chronic GVHD; solid line, no chronic GVHD.

On the basis of selection criteria, there were no significant differences in age, sex, donor sex or match, malignant diagnosis, stem cell source, conditioning intensity, or the occurrence of acute GVHD.

Although there was a trend toward a reduction in the overall rate of chronic GVHD when comparing rituximab-treated cases and controls (48% vs 60%, $P = .1$), the 2-year cumulative incidence of systemic corticosteroid-requiring chronic GVHD was 31% among rituximab-treated subjects and 48.5% among controls ($P = .015$) (Figure 3A). In a multivariable competing risks regression analysis, treating acute GVHD as a time-dependent variable, the use of rituximab (hazard ratio, 0.47; 95% confidence interal [CI], 0.23-0.99; $P = .046$) and myeloid disease (hazard ratio, 0.37; 95% CI, 0.17-0.79; $P = .01$) was significantly associated with protection from corticosteroid-requiring chronic GVHD, whereas age, donor-recipient sex matching, donor type, conditioning intensity, disease relapse index, and acute GVHD had no statistically significant influence.

The 4-year cumulative incidence of nonrelapse mortality was 19% in the control population, in comparison with 5.1% in rituximab-treated subjects ($P = .02$). Of 4 subjects who died of nonrelapse causes in the rituximab cohort, the causes of death are chronic GVHD (3) and respiratory failure (1). Of 13 patients who died of nonrelapse causes in the control cohort, the causes of death are chronic GHVD (8) and cardiac, traumatic, secondary malignancy, respiratory failure, and unknown (1 each). Of these 13, 10 developed chronic GVHD prior to death. The 4-year cumulative incidence of relapse was no different between rituximab-treated patients and controls (34% vs 28%, $P = .79$) (Figure 3B), even when stratified by CD20 status. PFS at 4 years was no different (61% vs 53%, $P = .27$); however, 4-year OS was significantly higher in rituximab-treated subjects when compared with controls (71% vs 56%, $P = .05$) (Figure 3C). In a multivariable Cox regression analysis examining the same potential variables as for the occurrence of steroid-requiring chronic GVHD, the use of rituximab (hazard ratio for death, 0.56; 95% CI, 0.31-1.00; $P = .048$) and high or very high disease relapse index

Discussion

Several lines of evidence implicate B cells in the pathophysiology of chronic GVHD.[32,33] In this clinical trial, we have demonstrated that the posttransplantation administration of rituximab is safe and reduces the incidence of systemic corticosteroid-requiring chronic GVHD when compared with concurrent controls. Although the overall rate of chronic GVHD was only modestly affected and did not attain the 20% reduction hypothesized, the majority of patients treated with prophylactic rituximab who were affected had only mucocutaneous disease that did not require systemic therapy and was not associated with excess transplant-associated mortality. In fact, we noted an extremely low rate of transplant-associated mortality of 5% at 4 years from transplantation in a landmark analysis of patients who were enrolled in this clinical trial 3 months after transplantation.

This clinical trial did not use the National Institutes of Health (NIH) Staging System for the diagnosis and severity assessment of chronic GVHD because the trial was conceived before the NIH diagnostic system was initially published,[34] and long before this staging system was validated.[35-37] Similarly, the recommendations from the NIH Consensus Conference for the conduct of clinical trials in chronic GVHD was not published until after the initiation of this trial.[38] Faced with the lack of a standardized and recognized marker of chronic GVHD severity, we chose 2 end points to measure the efficacy of our intervention: the occurrence of any-degree chronic GVHD by clinician assessment, and the requirement of systemic corticosteroids specifically to treat chronic GVHD, as a surrogate for chronic GVHD severity. We felt this latter end point was valid because chronic GVHD involving mucocutaneous tissues treated with topical therapy alone generally does not impact posttransplantation survival. In acute GVHD clinical trial designs in which corticosteroid-sparing strategies are being tested, it is recommended that corticosteroid doses be incorporated into the outcome assessment, providing further justification for this end point.[39] It

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