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Establishment of Early Donor Engraftment after Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplantation to Potentiate the Graft-versus-Lymphoma Effect against Refractory Lymphomas

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ABSTRACT

Reduced-intensity allogeneic hematopoietic stem cell transplantation (alloHSCT), which typically results in mixed chimerism initially after transplantation, has had limited efficacy in chemotherapy-refractory lymphomas. We hypothesized that the rapid establishment of complete donor chimerism would potentiate a graft-versus-lymphoma effect. Fifteen patients with chemotherapy-refractory lymphoma initially received induction with a conventional chemotherapy regimen (etoposide, prednisone, vincristine, cyclophosphamide, adriamycin, fludarabine [EPOCH-F]) to deplete host T cells and provide disease control prior to alloHSCT. Patients then received conditioning with fludarabine and cyclophosphamide followed by alloHSCT from HLA-matched siblings. Graft-versus-host disease prophylaxis consisted of cyclosporine alone. EPOCH-F resulted in 73% of patients having partial responses or stable disease. EPOCH-F depleted host CD4$^+$ T cells from a median of 235 cells/μL to 56 cells/μL. Fourteen patients underwent alloHSCT, and all had >95% donor engraftment by day 14 after transplantation. The incidence of Grade II to III acute graft-versus-host disease was 71%. There were two therapy-related deaths. There were 8 partial responses and 3 complete responses (CRs) at day 28. Five additional CRs were observed at day 100 without withdrawal of cyclosporine or donor lymphocyte infusion. The rate of CRs for all 15 patients was 60%. The 1-year progression-free survival rate from time of study entry is 67% with only 1 relapse among 9 CRs. At a median potential follow-up of 28 months, the overall survival rate is 53%. These data demonstrate that a potent and durable graft-versus-lymphoma effect can occur against chemotherapy-refractory lymphomas and suggest that this effect may be associated with rapid, complete donor chimerism after reduced-intensity alloHSCT.

KEY WORDS

Non-Hodgkin's lymphoma • Allogeneic • Reduced intensity • Chimerism

INTRODUCTION

Patients with chemotherapy-refractory lymphomas who fail to enter a remission with initial chemotherapy (primary refractory) or to achieve a partial response to second-line or "salvage" chemotherapy at relapse (secondary refractory) have a very poor prognosis [1-3]. High-dose therapy and autologous hematopoietic stem cell transplantation (autoHSCT) appear to benefit only a small minority of patients with primary or secondary refractory B-cell lymphomas [4-6]. As such, there is a need for novel, alternative therapies in this poor prognostic group.

Allogeneic hematopoietic stem cell transplantation (alloHSCT), using myeloablative conditioning regimens, may provide durable remissions in patients with refractory lymphomas [7-11]. However, the applicability of alloHSCT has been severely limited by treatment-related morbidity and mortality in older adults and in younger patients who have received extensive

prior therapy or have a less than optimal performance status, which often negate the beneficial effects of alloHSCT [10-13]. Attempts to reduce treatment-related mortality have been made by using nonmyeloablative or reduced-intensity (RI) conditioning regimens that are adequately immunosuppressive to consistently permit the engraftment of allogeneic stem cells from HLA-matched siblings [14-18]. RI alloHSCT relies either primarily or almost exclusively on a graft-versus-lymphoma (GVL) effect to eliminate lymphoma. Specifically, this strategy typically produces a state of mixed chimerism, which may compromise the GVL effect, and often necessitates the removal of immunosuppressive agents, such as cyclosporine (CsA), and/or the infusion of additional donor lymphocytes to convert the recipient to full donor lymphoid chimerism [17-19]. The efficacy of RI alloHSCT has been limited in lymphomas that are refractory, bulky, or of advanced histology [20-27]. We hypothesized that establishment of rapid and complete donor chimerism after RI alloHSCT would enhance the GVL effect in patients with chemotherapy-refractory lymphomas.

Based on a murine F1-into-parent model of marrow graft rejection [28], we designed a protocol that uses repeated cycles of chemotherapy at conventional doses to deplete host T cells to a level that might limit mixed chimerism after RI alloHSCT. The primary aim of this study was to determine whether this sequential chemotherapy approach, which emphasizes the role of host immune ablation, would permit rapid complete donor chimerism after alloHSCT in the treatment of refractory B-cell lymphomas.

PATIENTS AND METHODS

Eligibility Criteria

Patients with non-Hodgkin's lymphoma (NHL) or chronic lymphocytic leukemia that was primary or secondary chemotherapy-refractory or had progressed after autoHSCT were eligible for this study. Diagnosis was confirmed by the National Cancer Institute (NCI) Laboratory of Pathology using the Revised European-American Lymphoma (REAL) classification [29]. Age between 16 and 75 years, Karnofsky performance status of >70%, serum bilirubin <2.5 mg/dL, hepatic transaminases ≤2.5 times normal, creatinine clearance >60 mL/min, pulmonary diffusion capacity >50% of predicted, and left ventricular ejection fraction of >50% were additional eligibility criteria. All patients had an acceptable 5 of 6 or 6 of 6 HLA-matched sibling donor who consented to serve as an allogeneic blood stem cell donor. This protocol, CC 99-C-0143, was approved by the NCI Institutional Review Board, and informed written consent was obtained from each patient and their respective donor.

Induction Chemotherapy

To reduce circulating T cells while providing tumor control prior to transplantation, patients received an induction regimen—etoposide, prednisone, vincristine, cyclophosphamide, adriamycin, fludarabine (EPOCH-F)—that combines fludarabine with the EPOCH regimen, which has been shown to be active in refractory lymphomas [30]. Patients received a minimum of 1 and a maximum of 3 cycles of EPOCH-F, which was administered every 21 days. Patients received EPOCH-F until their CD4 count was <50 cells/μL or until progressive disease occurred after any given cycle. EPOCH-F consisted of a 72-hour (days 1 to 3) continuous infusion of etoposide (50 mg/m^2/d), doxorubicin (10 mg/m^2/d), vincristine (0.5 mg/m^2/d), cyclophosphamide (600 mg/m^2) intravenously (IV) on day 4, prednisone 60 mg/m^2/d orally on days 1 to 4, and fludarabine (25 mg/m^2/d) IV on days 1 to 3. Filgrastim (granulocyte colony-stimulating factor) was given subcutaneously 10 μg/kg/d from day 5 until an absolute neutrophil count (ANC) >1000 cells/μL for 2 consecutive days.

Conditioning Regimen

The conditioning regimen consisted of fludarabine (30 mg/m^2/d) and cyclophosphamide (1200 mg/m^2/d) administered concomitantly IV on days -6, -5, -4, and -3 prior to transplantation. Sodium 2-mercaptoethanesulfonate (Mesnex, Bristol-Myers Squibb/Baxter Healthcare, Deerfield, IL) was given on days -6 to -3 by continuous IV infusion at a dosage of 1200 mg/m^2/d.

Blood Stem Cell Mobilization, Collection, and Transplantation

Hematopoietic stem and progenitor cells were mobilized with filgrastim at 10 μg/kg/d. Apheresis was performed on days 5 and 6 of filgrastim administration using the Fenwal CS3000 Plus cell separator (Baxter Healthcare Corporation, Deerfield, IL). Fifteen to 25 L of blood were processed per procedure to achieve a target dose of 4.0×10^6 CD34$^+$ cells/kg (recipient weight). All apheresis products were cryopreserved in Plasmalyte A (Baxter) with 4% human serum albumin, 5% dimethyl sulfoxide (Research Industries, Salt Lake City, UT), and 6% Pentastarch (B. Braun, Irvine, CA), and were stored in liquid nitrogen. Cells were thawed and infused on day 0. Filgrastim was administered daily at 10 μg/kg from the day of alloHSCT until the ANC was >5000 cells/μL for 3 consecutive days.

Graft-versus-Host Disease Prophylaxis

Patients received CsA alone as graft-versus-host disease (GVHD) prophylaxis. CsA was initiated on day -1 of the transplantation and was adjusted to maintain trough serum CsA levels of 150 to 250 ng/mL for the first 100 days after alloHSCT and then tapered between day +100 and +180, depending on the presence or absence of GVHD.

Supportive Care

Following both induction chemotherapy and transplantation, infection prophylaxis consisted of trimethoprim/sulfamethoxazole, acyclovir, and fluconazole. To avoid potential drug interactions with vincristine, fluconazole was held during the administration of EPOCH-F. Trimethoprim/sulfamethoxazole was given for the week prior to stem cell transplantation, and then was resumed each weekend day after engraftment.

Quantitation of Host Immune T-Cell Depletion

The absolute number of circulating host CD4$^+$ and CD8$^+$ T cells were determined at study entry, after day 17 of each cycle of EPOCH-F, and on the day of stem cell infusion (day 0). Flow cytometry was performed in a Clinical Laboratory Improvement Amendments–certified laboratory (Science Applications International Corporation, Frederick, MD). The percentage of CD45$^+$ lymphocytes expressing CD3$^+$CD4$^+$ or CD3$^+$CD8$^+$ markers was determined. Complete blood cell counts and differentials, performed in the National Institutes of Health Clin-

Table 1. *Patient Characteristics*

Patient No.	Age	Sex	Histology	No. of Prior Tx	Prior AutoHSCT	Disease Status at Study Entry	CD4+/CD8+ # Pre-EPOCH-F	CD4+/CD8+ # Post-EPOCH-F
1	44	M	MC	3	Yes	Refrac relapse	74/48	16/5
2	38	M	FCC	5	Yes	Refrac relapse	283/160	78/25
3	41	F	DLC	4	No	Refrac relapse	118/156	49/58
4	33	F	Thymic DLC	2	No	Primary refract	235/406	26/12
5	34	F	DLC	3	No	Refrac relapse	13/13	12/12
6	51	M	MC	1	No	Untreated relapse	365/599	56/104
7	51	M	CLL (PLL)	6	No	Refrac relapse	1697/849	48/2
8	39	M	MC	3	No	Refrac relapse	267/934	141/309
9	63	F	FCC	4	No	Refrac relapse	196/302	77/102
10	61	F	DLC	3	Yes	Refrac relapse	172/124	54/32
11	39	F	DLC	3	No	Primary refract	285/462	102/68
12	49	F	FCC	3	No	Sens relapse	91/51	62/40
13	52	M	CLL	4	No	Refrac relapse	522/161	165/22
14	57	F	FCC	2	No	Refrac relapse	439/248	96/31
15	56	M	DLC	1	No	Prim refract	141/39	10/2

Tx indicates treatment; CMV, cytomegalovirus; AutoHSCT, autologous hematopoietic stem cell transplant; #, cells/mL; EPOCH-F, etoposide/prednisone/vincristine/cyclophosphamide/adriamycin/fludarabine; M, male; F, female; MC, mantle cell; Refrac relapse, refractory relapse; FCC, follicular center cell; DLC, diffuse large cell; Primary refract, primary refractory; PLL, prolymphocytic leukemia; CLL, chronic lymphocytic leukemia; +, positive serology; −, negative serology; NA, not available.

ical Center Laboratory, were then used to calculate the absolute number of $CD4^+$ and $CD8^+$ T cells per μL of blood.

Chimerism Evaluation

Chimerism analysis was performed using the variable number tandem repeats–polymerase chain reaction method in a Clinical Laboratory Improvement Amendments–certified laboratory at the Blood Center of Southeastern Wisconsin. Chimerism was determined at day +14, day +28, day +56, day +100, and day +365 posttransplantation on total peripheral blood mononuclear cells. In some cases, chimerism was additionally determined on posttransplantation samples enriched for myeloid ($CD15^+$ or $CD33^+$) or T-lymphoid ($CD3^+$) subsets. Myeloid or lymphoid cell subset enrichment was by positive selection using either magnetic beads (Miltenyi, Inc., Auburn, CA) or rosette technique (Stem Cell Technologies, Inc., Vancouver, Canada).

Definitions of Response

Disease response was assessed according to the recommendations of the NCI Sponsored International Working Group for the standardization of response criteria for NHL [31]. Stable disease was defined as no more than a 25% increase or a 25% decrease in the sum products of the greatest diameters of lymph nodes and nodal masses. All patients underwent a computerized axial tomography of the chest, abdomen, and pelvis and a bone marrow examination prior to study entry, after each cycle of EPOCH-F, and at day +28, day +100, +6 months, +9 months, +12 months, and thereafter annually unless otherwise clinically indicated. Single-photon emission computed tomography was used to assess questionable abnormalities.

Statistical Analysis

Toxicities were defined using the NCI Toxicity Criteria Version 2.0. Progression-free survival (PFS) was calculated from the date the patient enrolled in the study, as well as the date of transplantation, until the date that the patient progressed or had progression censored at the date of death or last follow-up. Survival durations were calculated from enrollment date until date of death or last follow-up. The probabilities of survival or PFS as a function of time were calculated using the Kaplan-Meier method [32]. Associations between categorical parameters and response were made using the Jonckheere-Terpstra trend test or Cochran-Armitage trend test depending on whether both variables or only one variable was ordered [33,34]. In addition, changes in response at set time points in the treatment course were compared with the initial response using a marginal homogeneity test, which is an extension of McNemar's test for paired categorical data [35]. In each case, an exact method was used due to the small number of patients evaluated. All reported *P* values are two-tailed.

RESULTS

Patient Characteristics

Fifteen patients were enrolled between July 1999 and October 2000 (Table 1). The median patient age was 49 years (range: 33 to 63 years). Histologies included large cell B-cell lymphoma in 6, follicular B-cell lymphoma in 4, mantle cell lymphoma in 3, and chronic lymphocytic lymphoma in 2, including 1 that had transformed to prolymphocytic leukemia [29]. Thirteen patients had disease that was refractory to the last administered regimen, including 3 patients with primary refractory NHL. One patient with mantle cell lymphoma was enrolled following relapse after "hyper–cyclophosphamide, vincristine, doxorubicin, dexamethasone" [36]. The median number of prior therapies was 3 (range: 1 to 6), and 3 patients had received a prior autoHSCT.

Host Immunoablation

The median $CD4^+$, $CD8^+$, and natural killer cell numbers prior to treatment were 235 (range: 13 to 1697), 161 (range: 13 to 934), and 69 (range: 23 to 283) cells/mL, respectively (Table 1). Patients received a median of 2 cycles (range: 1 to 3) of

Table 2. *Posttransplantation Outcome*

Patient No.	Engraftment (VNTR-PCR Analysis of Total MNC) Day +14	Day +28	Day +56	Day +100	Day +365	GVHD Acute	Chronic	Current Status After AlloHSCT
1	98%	99%	100%	100%	100%	Gr II	Extensive	Alive +30 mo, isolated relapse at 24 mo
2	100%	100%	100%	—	NE	Gr III	Extensive	Died d +153 from gastrointestinal bleed (GVHD)
3	98%	100%	100%	100%	100%	Gr II	Limited	Alive +26 mo, CR
4	100%	100%	100%	100%	NE	Gr II	None	Died d +134 from PD
5	98%	100%	100%	100%	100%	Gr I	Extensive	Alive +26 mo, CRu
6	100%	100%	100%	100%	100%	Gr III	None	Alive +23 mo, CR
7	95%	95%	—	100%	NE	Gr III	Extensive	Died d +236 from infection (Aspergillus) with SD
8	95%	80%*	75%*	75%	100%	Gr II	None	Alive +21 mo, CR
9	95%	98%*	100%	100%	NE	Gr I	None	Died d +120 from PD
10	100%	100%*	NE	—	—	Gr III	NE	Died d +73 from PD
11	100%	99%	100%	100%	NE	Gr III	None	Died d +191 from PD
12	100%*	100%	100%	100%	100%	Gr I	Limited	Alive +17 mo, CRu
13	99%*	100%	100%	100%	100%	Gr II	Extensive	Alive +16 mo, CRu
14	100%*	100%*	100%	100%	100%	Gr I	None	Alive +15 mo, CRu

MNC indicates mononuclear cells; GVHD, graft-versus-host disease; mo, months; Gr, grade; CR, complete response; CRu, complete response undetermined; PD, progressive disease; SD, stable disease; NE, non-evaluable.

*Complete (x ≥ 98%) lymphoid chimerism by CD3 separation.

EPOCH-F, and the median $CD4^+$ and $CD8^+$ cell numbers after EPOCH-F were of 56 (range: 10 to 165; $P = .03$) and 31 (range: 2 to 309; $P = .01$) cells/mL, respectively. Circulating natural killer cell numbers (median , 90; range: 21 to 413) were not significantly ($P = .76$) reduced after EPOCH-F. Three patients proceeded to transplantation with CD4 counts >50 cell/mL, despite receiving less than 3 cycles of EPOCH-F, due to progressive disease.

Hematopoietic Recovery

Fourteen patients proceeded to transplantation and all were evaluable for hematopoietic recovery and engraftment. Patients received a median of 8.08×10^6 $CD34^+$ cells/kg (range: 4.55 to 12.8×10^6) and 3.50×10^8 $CD3^+$ cells/kg (range: 2.12 to 7.85×10^8). The median times to an ANC >500, 1000, and 5000×10^9/L were 9, 9, and 10.5 days, respectively. All but 1 patient achieved a platelet count $>100 \times 10^3$/L. The median times to platelet counts of 20, 50, and 100×10^3/L were 9.5, 13, and 15 days, respectively, independent of platelet transfusion.

Donor Lymphoid and Myeloid Engraftment

All 14 patients demonstrated evidence of near complete donor chimerism at day +14 posttransplantation; the median total mononuclear cell donor chimerism was 98% (Table 2). Lymphoid chimerism was complete and sustained as measured on days +28 through +365. No patient received a donor lymphocyte infusion.

Toxicity

Induction Chemotherapy with EPOCH-F. A total of 31 cycles of EPOCH-F was administered. The regimen was well tolerated with only 3 episodes of neutropenic fever. Two patients developed active infections prior to alloHSCT, 1 with a respiratory syncitial virus pneumonitis, which resolved with ribavirin, and 1 with a pulmonary aspergillosis, which resolved with amphotericin. The case of pulmonary aspergillosis progressed in the central nervous system, but responded to therapy with voriconazole [37].

Conditioning Regimen with Fludarabine and Cyclophosphamide. Patients experienced minimal to no mucositis, and there were no cases of veno-occlusive disease. The most significant toxicity was engraftment syndrome, defined by the occurrence of pulmonary infiltrates, third-spacing of fluids, and fever, which was observed in 6 patients (43%) [38]. Patients with engraftment syndrome received systemic corticosteroids (methylprednisolone 1 g/d in divided doses). All patients had complete resolution of symptoms, generally within 24 to 72 hours after initiation of corticosteroids, which were then tapered rapidly to discontinuation over a 1- to 2- week period.

Acute and Chronic GVHD

Fourteen patients were evaluable for acute GVHD (Table 2), and 10 (71%) patients developed Grade II to III acute GVHD. There were no cases of Grade IV acute GVHD. The median time to onset of acute GVHD was 31 days (range: 11 to 84 days). In 3 of the 5 patients with Grade III acute GVHD, the onset of disease occurred after discontinuation of CSA on account of either toxicity ($n = 2$) or progressive lymphoma ($n = 1$). Seven of 13 (54%) evaluable patients developed chronic GVHD. Two patients had limited chronic GVHD, and 5 patients had extensive chronic GVHD. The 2 treatment-related mortalities (gastrointestinal bleed and Aspergillus infection) were directly related to GVHD, as both patients were receiving corticosteroids at the time of death.

Outcome

All patients received at least 1 cycle of EPOCH-F. After receiving EPOCH-F, 5 patients achieved a partial response, including 3 patients whose disease was previously chemotherapy-refractory. Six patients had stable disease, and 4 patients had progressive disease.

Fourteen patients proceeded to alloHSCT. One patient with primary refractory disease (patient 15) progressed during EPOCH-F and did not proceed to alloHSCT. Response was determined at day +28 after alloHSCT to evaluate the cytotoxic effects of the conditioning regimen. The overall response at day +28 was 73% with 3 complete responses (CRs) and 8 partial responses. Between day +29 and day +100 posttransplantation 5 additional patients had a CR. One patient with stable disease at day +28 and a partial response at day +100, subsequently achieved a CR at 6 months after alloHSCT. All 3 patients, who had progressed on EPOCH-F and achieved a partial response at day +28, had progressive disease at day +100. The overall response rate for this treatment approach, on an intent-to-treat basis, was 80% with 9 CRs and 3 partial responses. At a median potential follow-up of 28 months (range: 19 to 37) from the time of study entry, the PFS rate is 67% at 1 year on an intent-to-treat analysis (Figure 1A). The overall survival rate is 53% (Figure 1B). Of the 9 patients who made it to CR (8 by day +100 and 1 by 6 months), all were still without progression from 20 to 31 months after transplantation, except for 1 patient who progressed 26.5 months after transplantation.

There was no significant association of response to the number of previous regimens, including prior autoHSCT, or histology. There was a strong association between response to EPOCH-F and response after alloHSCT. All 5 patients who achieved a partial response to EPOCH-F eventually achieved a CR after alloHSCT, as compared with only 4 of 9 patients who had stable or progressive disease to EPOCH-F ($P = .0005$). There was no association between the development of GVHD and best response ($P > .05$).

DISCUSSION

In contrast to a strategy of establishing mixed chimerism, we chose to achieve rapid, complete donor chimerism through the administration of sequential, immunoablative chemotherapy. We chose this strategy for two reasons. First, the available medical literature suggests that an optimal graft-versus-tumor effect may not be observed until complete lymphoid chimerism is achieved [24,25,39]. Second, we targeted patients with aggressive, chemotherapy-refractory lymphomas. A strategy of establishing mixed chimerism may be adequate for less aggressive, relatively indolent lymphomas [40]. The proliferation of more aggressive lymphomas, however, such as mantle cell or large B-cell NHL, may outpace the establishment of complete donor chimerism and subsequent GVL effects. One tactic that provides both significant anti-tumor activity and rapid, complete donor chimerism is high-dose therapy and autoHSCT prior to RI alloHSCT [41]. We elected to administer immunoablative chemotherapy at conventional doses and, adopting a tactic used by investigators at M.D. Anderson Cancer Center, used chemotherapeutic agents that had activity against the disease being treated [26,27,40]. The EPOCH-F regimen resulted in a decrease in circulating T lymphocytes in all patients and provided disease control in the majority of patients. The effectiveness of this strategy on engraftment was realized as all patients had complete lymphoid chimerism by day +28 posttransplantation. The fact that all patients had complete engraftment does not permit us to make any firm conclusions relative to our hypothesis; however, an ongoing clinical trial with T-cell–depleted allografts strongly suggests that host T-cell depletion before transplantation is important relative to the achievement of complete donor chimerism [42].

Although the patient numbers are small, the CRs are relatively high in this select group of patients with refractory lymphomas, who were all ineligible for autoHSCT. These responses could partially be attributed to the conditioning regimen, which contained agents that are active against lymphomas and were used at higher than conventional doses [43]. However, the majority of CRs occurred between day +28 and day +100. Delayed responses, such as these, have been observed after high-dose cytotoxic chemotherapy and autologous stem cell transplantation. In light of the fact that all of these patients had received extensive prior therapy, however, that the majority had less than a partial response to EPOCH-F and that responses have been sustained suggest that these responses are at least partially attributable to a GVL effect [44]. The contributions of this significant dose of cyclophosphamide, however, as well as fludarabine, can not be dismissed. These results are in contrast to other reports of RI alloHSCT for the treatment of lymphomas, where responses were typically delayed and did not occur until withdrawal of immune suppression, and/or required donor lymphocyte infusions [17,18]. This treatment strategy also was associated with a high incidence of clinically significant acute and chronic GVHD. Although there was not a direct correlation between the development of GVHD and response, all complete responders had some form of GVHD. It should be noted that in 3 patients with progressive disease GVHD did not occur until removal of CsA to permit a GVL effect, but this tactic was unsuccessful. It also should be noted that the 2 treatment-related mortalities were indirectly related to GVHD because they were clearly related to chronic corticosteroid administration. Although direct comparisons can not be made to previous reports, these data demonstrate that complete and durable responses can occur after RI alloHSCT in patients with chemotherapy-refractory disease [45].

These results support our hypothesis that rapid, complete donor engraftment can result in high response rates for relapsed, refractory B-cell lymphomas. Responses were observed in more advanced NHL, such as large cell and mantle cell NHL; however; it is not clear whether this strategy is necessary in patients with more "indolent" disease [40]. Also, the amount of prior cytotoxic therapy may be adequately immunosuppressive to result in engraftment kinetics similar to the results observed in this study. A strategy of sequential, immunoablative chemotherapy with activity against lymphomas can result in adequate disease control and rapid, complete donor engraftment. The engraftment results were consistent, and this strategy does not require the relatively precarious management of mixed chimerism requiring withdrawal of immune suppression or the infusion of additional donor lymphocytes [15,17,18]. The establishment of rapid donor chimerism more closely reflects the engraftment kinetics associated with "traditional," myeloablative alloHSCT while avoiding early toxicities associated with myeloablative conditioning regimens. Similar to myeloablative transplanta-

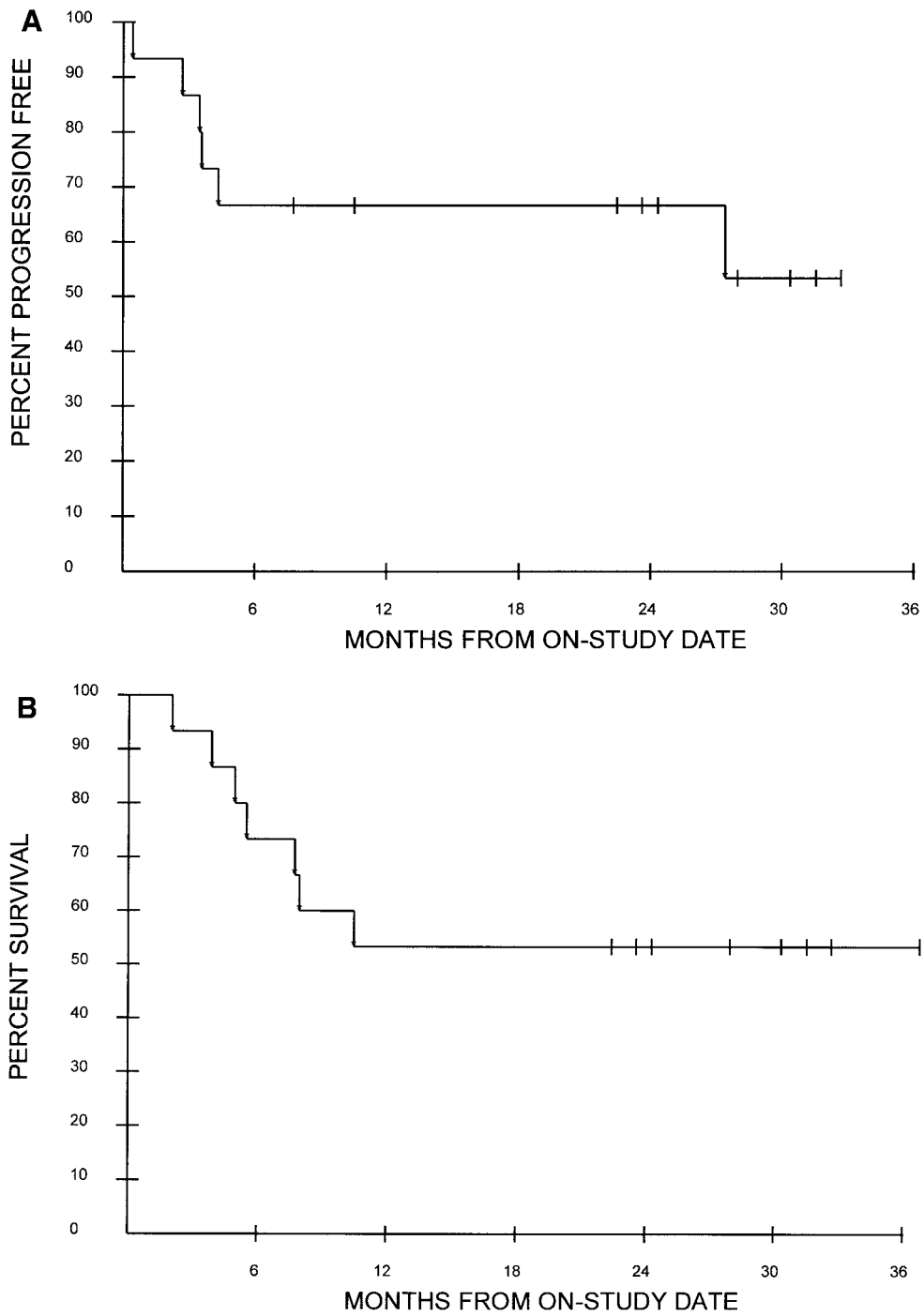

Figure 1. (A) PFS for all 15 patients with B-cell lymphomas enrolled in the study. (B) Overall survival for all 15 patients with B-cell lymphomas enrolled in the study.

tions, however, significant toxicities persist primarily in the form of GVHD. The decision to use myeloablative, RI, or nonmyeloablative allogeneic transplantation for lymphomas should take into account disease status, histology, and degree of prior therapy. Immunoablative strategies that provide disease control and result in rapid complete lymphoid chimerism should be considered in the use of RI alloHSCT for patients with advanced, refractory B-cell lymphomas.

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