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Low Risk of Chronic Graft-versus-Host Disease and Relapse Associated with T Cell–Depleted Peripheral Blood Stem Cell Transplantation for Acute Myelogenous Leukemia in First Remission: Results of the Blood and Marrow Transplant Clinical Trials Network Protocol 0303

Steven M. Devine,[1] Shelly Carter,[2] Robert J. Soiffer,[3] Marcelo C. Pasquini,[4] Parameswaran N. Hari,[4] Anthony Stein,[5] Hillard M. Lazarus,[6] Charles Linker,[7] Edward A. Stadtmauer,[8] Edwin P. Alyea, III,[3] Carolyn A. Keever-Taylor,[4] Richard J. O'Reilly[9]

Graft-versus-host disease (GVHD) is most effectively prevented by ex vivo T cell depletion (TCD) of the allograft, but its role in the treatment of patients undergoing allogeneic hematopoietic cell transplantation (HCT) for acute myelogenous leukemia (AML) in complete remission (CR) remains unclear. We performed a phase 2 single-arm multicenter study to evaluate the role of TCD in AML patients in CR1 or CR2 up to age 65 years. The primary objective was to achieve a disease-free survival (DFS) rate of >75% at 6 months post-transplantation. A total of 44 patients with AML in CR1 (n = 37) or CR2 (n = 7) with a median age of 48.5 years (range, 21-59 years) received myeloablative chemotherapy and fractionated total body irradiation (1375 cGy) followed by immunomagnetically selected CD34-enriched, T cell–depleted allografts from HLA-identical siblings. No pharmacologic GVHD prophylaxis was given. All patients engrafted. The incidence of acute GVHD grade II-IV was 22.7%, and the incidence of extensive chronic GVHD was 6.8% at 24 months. The relapse rate for patients in CR1 was 17.4% at 36 months. With a median follow-up of 34 months, DFS for all patients was 82% at 6 months, and DFS for patients in CR1 was 72.8% at 12 months and 58% at 36 months. HCT after myeloablative chemoradiotherapy can be performed in a multicenter setting using a uniform method of TCD, resulting in a low risk of extensive chronic GVHD and relapse for patients with AML in CR1.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the most effective means for preventing relapse in patients with acute myelogenous leukemia (AML) in complete remission (CR) [1-5]. However, both acute and chronic graft-versus-host disease (GVHD) frequently occur after HCT and adversely affect quality of life and overall survival [1,6-8]. GVHD is most commonly prevented by pharmacologic therapy, but is most effectively prevented by ex vivo T cell depletion (TCD) of the allograft [9,10]. However, the use of TCD is limited by logistical difficulties, lack of a Food and Drug Administration (FDA)-approved method, and concerns regarding potential risks of graft rejection, posttransplantation infection, and leukemic relapse. Nonetheless, several recent TCD studies involving patients with AML suggest a low risk of GVHD and relapse with this approach, particularly

From the [1]Medicine Department of Ohio State University, Columbus, Ohio; [2]EMMES Corporation, Rockville, Maryland; [3]Dana-Farber Cancer Institute, Boston, Massachusetts; [4]Medical College of Wisconsin, Milwaukee, Wisconsin; [5]City of Hope, Duarte, California; [6]University Hospitals Case Medical Center, Cleveland, Ohio; [7]University of California, San Francisco, California; [8]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, Pennsylvania; and [9]Memorial Sloan-Kettering Cancer Center, New York, New York.

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Correspondence and reprint requests: Steven M. Devine, MD, B316 Starling-Loving Hall, 320 W 10th Ave, Columbus, OH 43210 (e-mail: steven.devine@osumc.edu).

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in patients undergoing HCT while in remission [11-15].

The goal of the present study was to determine whether the encouraging results reported by single centers could be reproduced in a multicenter setting. We selected a TCD method that would remove almost all T cells and thus eliminate the need for posttransplantation pharmacologic GVHD prophylaxis. We limited enrollment to adult patients with AML in first CR (CR1) or second CR (CR2) and administered the TCD graft after an intensive pretransplantation conditioning regimen, reasoning that the potentially undesirable effects of TCD (eg, graft rejection, relapse) would be reduced if combined with a conditioning regimen that is highly immunosuppressive and antileukemic. Our results demonstrate the feasibility and effectiveness of this uniform approach.

METHODS

Patients and Donors

Patients aged 18-65 years with a diagnosis of AML in first or second complete morphological remission (CR1 or CR2) according to International Working Group criteria were eligible for this study [16,17]. Patients with acute promyelocytic leukemia and t(15;17) or core binding factor AML [M4Eo with inv16 and AML with t(8;21)] in CR1 were not eligible. Patients had to have a HLA-identical sibling donor willing to consent and able to donate a granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem/progenitor cell (PBSC) allograft and normal organ function, and had to be HIV-negative.

Sibling donors had to be younger than 75 years, weigh more than 25 kg, and be seronegative for human immunodeficiency virus, hepatitis B/C virus, human T-lymphotropic virus I/II, and syphilis. Both patients and donors provided written informed consent in accordance with the Helsinki Declaration protocol for a study approved by the institutional review board at each participating institution. The study was also approved by the FDA under an Investigational Device Exemption (BB-IDE#11965), held by the National Heart, Lung, and Blood Institute, and was monitored by an independent Data Safety and Monitoring Board appointed by the National Heart, Lung, and Blood Institute. The clinical trial is registered at Clinical Trials.gov as NCT00201240.

Conditioning Regimen

All patients received a conditioning regimen consisting of hyperfractionated total body irradiation (TBI) at a total dose of 1375 cGy given over 4 days (on days -9, -8, -7, and -6) at a dose rate of <20 cGy/minute. Doses of 125 cGy/fraction were administered at a minimum interval of 4 hours between fractions, 3 times daily, for a total of 11 doses. Sequential doses of TBI were administered in an anterior/posterior or lateral orientation at the discretion of the radiation oncologists at each center, but the technique was kept consistent within each institution. Compensators and lung blocks yielding a minimum lung dose of 800 cGy were allowed based on institutional practice. After TBI, thiotepa was administered at a dose of 5 mg/kg (ideal body weight)/day i.v. for 2 days on days -5 and -4, followed by cyclophosphamide 60 mg/kg (ideal or adjusted body weight)/day for 2 days (days -3 and -2). A single 2.5 mg/kg dose of rabbit anti-thymocyte globulin (Thymoglobulin; Genzyme, Cambridge, MA) was given as an i.v. infusion over 6-8 hours on day -4.

Donor Mobilization and TCD Procedures

Donors received at least 5 consecutive doses of G-CSF 10-16 μg/kg once daily by s.c. injection. Leukapheresis was initiated on day 5 of G-CSF therapy. To maximize the $CD34^+$ cell dose transplanted, 2 consecutive days of leukapheresis (days 5 and 6) were planned for all donors. A third day of leukapheresis was allowed if necessary to ensure infusion of a minimum $CD34^+$ cell dose (see the next section).

$CD34^+$ cell selection with the Miltenyi CliniMACS device (Miltenyi Biotec, Bergisch Gladbach, Germany) was the sole method of TCD used in this clinical trial. TCD was performed in accordance with procedures outlined in the CliniMACS user's operating manual, as well as institutional standard operating procedures validated at each study site. Leukapheresis products were either processed on the same day as collected or refrigerated overnight (at 1-8°C) and processed the next morning.

Target Allograft Composition

The target allograft cell composition following TCD was a $CD34^+$ cell dose of $\geq 5.0 \times 10^6$/kg recipient weight in combination with a $CD3^+$ cell dose $< 1.0 \times 10^5$/kg recipient weight. A $CD34^+$ cell dose of 1.0×10^6/kg was the absolute minimum at which a recipient could still be considered evaluable for study endpoints. If this minimal dose was not achieved after 2 days of leukapheresis, then donors underwent a third collection. In that case, cells from the third collection were not to be $CD34^+$-selected. $CD34^+$-selected allografts were transplanted in accordance with institutional protocols on day 0 and sometimes also on day +1 post-HCT.

Supportive Care and Patient Assessment

The protocol specified that no posttransplantation pharmacologic GVHD prophylaxis would be given as long as the $CD3^+$ cell dose transplanted was $< 1.0 \times 10^5$/kg. Hematopoietic growth factors were not

routinely administered after HCT. Blood cytomegalovirus (CMV) surveillance was performed weekly with either quantitative polymerase chain reaction or antigenemia assay through day +100, and preemptive treatment was initiated as required according to institutional guidelines. Surveillance for Epstein-Barr virus (EBV) infection was performed weekly using a real-time quantitative EBV DNA polymerase chain reaction plasma-based assay through day +100 and then monthly up to day +180. EBV assays were sent from each center to a centralized laboratory at the University of Washington [18]. Patients with a blood EBV DNA concentration of >1000 copies/mL on any test were scheduled to receive preemptive rituximab at 375 mg/m^2 for at least 1 dose; rituximab was continued weekly if the concentration remained >1000 copies/mL after the first dose.

Acute and chronic GVHD were graded according to established criteria [19,20]. Patients were considered evaluable for GVHD if they engrafted. Organ toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0.

Donor hematopoietic chimerism was assessed on samples of unmanipulated bone marrow as well as on separated T cells (CD3$^+$) from peripheral blood obtained on days +28, +100, +180, and +365 using standard methods at each institution. Peripheral blood samples also were obtained for standard lymphocyte immunophenotyping at the same time points. No donor leukocyte infusions or other interventions were planned based on the results of the chimerism analyses.

Definitions

Neutrophil engraftment was defined as an increase in absolute neutrophil count to ≥500/μL for 3 consecutive days following a conditioning regimen-induced nadir. Platelet engraftment was defined as the first day of 3 consecutive platelet count measurements >50,000/μL without the aid of transfusion for 7 consecutive days. Primary graft failure was defined as failure of neutrophil engraftment by day +30. Secondary graft failure was defined as primary engraftment followed by a subsequent decline in the absolute neutrophil count to <500/μL with no apparent cause, such as drugs or opportunistic infection, and unresponsive to hematopoietic growth factor therapy.

The Southwest Oncology Group/Eastern Cooperative Oncology Group classification system was used to categorize the risk of relapse in patients with AML in CR1 based on cytogenetic findings [4]. Abnormalities not included in the Southwest Oncology Group/Eastern Cooperative Oncology Group definition were categorized according to the Cancer and Leukemia Group B classification system [21]. Patients with a normal karyotype at diagnosis found to have a Flt3 internal tandem duplication mutation were placed in the intermediate-risk cytogenetic category but were categorized as being at high risk for relapse based on previous studies [22,23].

Statistical Considerations

This study was a phase II single-arm multicenter trial with a primary objective of determining the disease-free survival (DFS) probability at 6 months post-HCT. This early DFS time point was chosen to begin planning for a follow-up trial to compare this approach with other GVHD prophylaxis strategies if the results appeared promising. DFS was defined as the minimum time from HCT to relapse or death, with censoring if the patient was alive and disease-free by May 10, 2010. The anticipated 6-month DFS probability was 75%, and the lower boundary for proceeding to a phase III trial was a DFS probability of >0.55. The primary hypothesis can be described as H_o: $P \leq .55$ versus H_1: $P > .55$. When the true DFS percentage is 75% with a sample size of 45, there is 84% power at $\alpha = .05$ to rule out a DFS percentage of <55%. Overall survival (OS) was defined as the time from HCT to death, with censoring if the patient was alive at the data cutoff date.

Kaplan-Meier estimates were computed for DFS and OS, with Greenwood's formula as the variance estimate [24]. Cumulative incidence curves incorporating death as a competing risk were computed for time to neutrophil and platelet engraftment, relapse, and acute and chronic GVHD [25]. The cumulative incidence of TRM was calculated with relapse as a competing risk. All calculations were performed using SAS version 9.1.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Patient and donor characteristics are presented in Table 1. A total of 47 patients were enrolled at 8 centers between October 2005 and December 2008. Three of these patients were enrolled but did not proceed to transplantation on this study due to withdrawal of informed consent (n = 2) or disease progression before the onset of conditioning (n =1); these 3 patients are not discussed further in this report. A total of 44 patients underwent HCT in this study.

Apheresis Products and Graft Processing

A total of 84 products were processed for the 44 patients who underwent HCT. Products from multiple days of collection were pooled for CD34-enrichment in 2 cases, and products from a single collection were split for enrichment on 2 columns in 4 cases. The results of the CD34$^+$ cell selection processing are presented in Table 2. All patients received >2.0 × 10^6

Table 1. Recipient and Donor Characteristics

Age, years, median (range)	48.5 (21-59)
Patient age by decade, n	
<20	0
20-29	7
30-39	4
40-49	14
50-59	19
Sex, n	
Male	16
Female	28
Performance status (KPS), n	
100%	17
90%	17
80%	8
70%	2
Leukemia stage, n	
CR1	37
CR2	7
Race, n	
White	42
Other	2
Cytogenetic risk (CR1/CR2), n	
Favorable	0/1
Intermediate	26/2
Unfavorable	11/3
Unknown	0/1
Recipient CMV serostatus positive/negative, n	17/27

$CD34^+$ cells/kg, and 86% received $>5.0 \times 10^6$/kg. No patient received more than the targeted $CD3^+$ cell dose of 1.0×10^5/kg.

Engraftment and Chimerism

All patients engrafted neutrophils and platelets, at a median of 12 days (range, 9-19 days) and 16 days (range, 13-159 days) posttransplantation, respectively. There were no primary graft failures. One female patient who underwent HCT while in CR1 using a male donor developed secondary graft failure on day +54 and later died of fungal pneumonia. No patient received a donor leukocyte infusion. Donor chimerism values are given in Table 3. The degree of donor chimerism was not predictive of relapse.

Immune Reconstitution

Quantitative recovery of lymphocytes is depicted in Figure 1. $CD4^+$ and $CD8^+$ reconstitution was slow, with median levels <200/μL until 1 year post-HCT.

Table 2. Results of CD34 Enrichment Procedures

TNC/product CD34 selected	7.2×10^{10} (2.1-15.5)
TNC processed/patient	13.4×10^{10} (5.4-26.9)
Total CD34 dose processed/patient	10.0×10^8 (2.9-34.6)
Final CD34 dose/kg transplanted	7.9×10^6 (2.4-31.3)
CD34 yield (%)/product CD34 selected	65.5% (27.2-125.5)
CD34 purity (%)/product CD34 selected	96.7% (61.5-99.8)
Total CD3 dose processed/patient	3.2×10^{10} (1.3-8.5)
Final CD3 dose/kg transplanted	6.6×10^3 (1.1-84.9)
Log_{10} T cell depletion/product CD34 selected	4.9 (3.2-5.9)

Data are median and range. The total number of products CD34 selected was 84.

Acute and Chronic GVHD

All patients were evaluable for acute GVHD. Ten patients developed grade II (n = 8) or III (n = 2) acute GVHD, and 10 patients developed grade I acute GVHD. No patient developed grade IV acute GVHD. Of the patients with grade II or III acute GVHD, 7 had gastrointestinal (GI) involvement (including 3 with upper GI involvement only), 6 had cutaneous involvement, and 2 had liver involvement. The median time to onset of any acute GVHD was 23 days (range, 14-100 days). The cumulative incidence of acute GVHD grade II-IV at 100 days was 22.7% (95% confidence interval [CI], 10.2%-35.3%) (Figure 2A). The cumulative incidence of acute GVHD grade III-IV at 100 days was 4.5% (95% CI, 0-10.8%) (Figure 2B). Eight patients developed chronic GVHD, at a median of 129 days post-HCT (range, 109-391 days). Chronic GVHD was limited in 5 patients and extensive in 3 patients. The cumulative incidence of any chronic GVHD was 19.0% at 24 months (95% CI, 6.8%-31.1%) (Figure 2C), and the cumulative incidence of extensive chronic GVHD was 6.8% (95% CI, 0-14.4%) at 24 months.

Opportunistic Infections

Thirty-four of the 44 patients (77%) experienced at least 1 documented infection. Bacterial infections were observed in 27 patients (61%); invasive fungal infections in 5 patients (11%); and viral infections (CMV or EBV) in 25 patients (57%). CMV viremia requiring preemptive treatment was observed in 11 patients (32%). Twenty-one patients were considered at high risk for CMV reactivation due to being CMV-seropositive (n = 17) or, if CMV-seronegative, having a seropositive donor (n = 4). Nine of these 21 patients (43%) developed CMV viremia. Eight patients (18%) developed EBV viremia (>1000 copies/mL), at a median of 114 days (range, 34-349 days) post-HCT, requiring at least 1 dose of rituximab (one 375-mg/m^2 dose in 7 patients and 4 doses in 1 patient). One patient developed posttransplantation lymphoproliferative disorder (PTLD) with a large-cell lymphoma involving the liver and died secondary to progressive donor cell–derived EBV-related PTLD on day +75. The cumulative incidence of EBV viremia at 12 months was 18.2% (95% CI, 6.6%-29.7%).

Nonhematologic Toxicity

The most common grade 3-5 nonhematologic toxicities related to the conditioning regimen were GI (mucositis/stomatitis) and pulmonary (Table 3).

Table 3. Results of Transplantation

Hematopoietic engraftment, days, median (range)	
Neutrophils	12 (9-19)
Platelets	16 (13-159)
Hematopoietic chimerism, donor %, median (range)	
T cell	
Day +28	95 (0-100)
Day +100	71 (0-100)
Day +180	80 (11-100)
Day +365	95 (0-100)
Myeloid	
Day +28	100 (75-100)
Day +100	100 (69-100)
Day +180	99 (8-100)
Day +365	100 (80-100)
Nonhematologic toxicity, % (grade) or number	
Mucositis/stomatitis	34% (3)
	5% (4)
Pulmonary	7% (3/4)
	5% (5)
Hepatic veno-occlusive disease	5% (mild)
	2% (moderate)
Thrombotic microangiopathy	2% (4)
Hemodialysis	n = 2
Seizures	n = 1
Acute GVHD (grade), cumulative incidence, % (95% CI)	
II-IV	23 (10-35)
III-IV	5 (0-11)
Chronic GVHD at 24 months, cumulative incidence, % (95% CI)	
Limited/extensive	19 (7-31)
Extensive only	7 (0-14)
Relapse, cumulative incidence, % (95% CI)	
All patients	
12 months	21 (8-33)
36 months	24 (11-37)
CR1 only	
12 months	14 (2-25)
36 months	17 (4-30)
CR2 only	
12 months	57 (15-99)
36 months	57 (15-99)
TRM, cumulative incidence, % (95% CI)	
12 months	14 (3-24)
36 months	23 (9-37)
DFS, Kaplan-Meier estimate, % (95% CI)	
All patients	
6 months	82 (70-93)
12 months	66 (52-80)
36 months	53 (37-69)
CR1 only	
12 months	73 (58-87)
36 months	58 (40-76)
CR2 only	
12 months	29 (0-68)
36 months	29 (0-68)
OS, Kaplan-Meier estimate, % (95% CI)	
All patients	
12 months	77 (65-90)
36 months	56 (40-73)
CR1 only	
12 months	81 (68-93)
36 months	60 (42-78)
CR2 only	
12 months	57 (17-98)
36 months	38 (0-84)

Transplantation-Related Mortality

Nine patients died from causes other than relapse, at a median of 188 days (range, 60-762 days) post-HCT. The cumulative incidence of transplantation-related mortality (TRM) was 14% (95% CI, 3.4%-24%) at 12 months, 20% (95% CI: 7.1-32.7) at 24 months, and 23.2% (95% CI: 9.3-37.1) at 36 months (Table 3).

Relapse, DFS, and OS

The median follow-up for all surviving patients was 34 months (range, 11.5-51.5 months). Ten patients relapsed (6 who underwent HCT in CR1 and 4 who underwent HCT in CR2), at a median of 198 days post-HCT (range, 74-664 days). The cumulative incidence of relapse for the entire group was 20.6% (95% CI, 8.4%-32.8%) at 12 months and 23.7% (95% CI, 10.5%-37%) at 36 months (Figure 3). Of the 10 patients who relapsed, 4 had intermediate-risk cytogenetics, 5 had high-risk cytogenics, and 1 had unknown cytogenics. The DFS rate at 6 months post-HCT was 81.8% (95% CI, 70.3%-93.4%) for the entire group. DFS and OS by stage are given in Tables 3 and Figure 4. The most common cause of death was relapse (Table 3).

DISCUSSION

These results demonstrate for the first time in a prospective multicenter setting that a strategy combining intensified myeloablative conditioning followed by transplantation of CD34-enriched, T cell–depleted PBSCs from HLA-identical sibling donors can result in consistent engraftment with a low risk of severe acute and chronic GVHD (<10% for both) and a low risk of relapse in patients with AML in CR1.

We chose a method for TCD that uses immunomagnetic selection of CD34-expressing cells based on previous studies that suggested reliable CD34 yields, high CD34 purity, and vigorous TCD [11,12,26,27]. The device (Miltenyi CliniMACS) was made available through an Investigational Device Exemption filed with the FDA. We have demonstrated that this method is highly reproducible from center to center, resulting in a consistently high degree of CD34 purification, TCD, and sterility. The CD34-enrichment procedure resulted in a median CD3 depletion of 4.9 logs. In all recipients, the CD3 dose was below the protocol-specified limit of 1×10^5/kg. The resulting low risk of grade II-IV and particularly grade III-IV acute GVHD despite the absence of pharmacologic GVHD prophylaxis suggests that this threshold T cell dose is appropriate in the HLA-matched sibling setting [28]. Although about 40% of patients still developed some acute GVHD, 13 of the 20 patients with acute GVHD had only cutaneous involvement which was manageable with corticosteroids. Further study is needed to determine whether this same threshold CD3 dose can be used in recipients of CD34-enriched unrelated donor PBSC grafts.

The median CD34 dose transplanted in this study was 7.9×10^6/kg, and, notably, 86% of the recipients

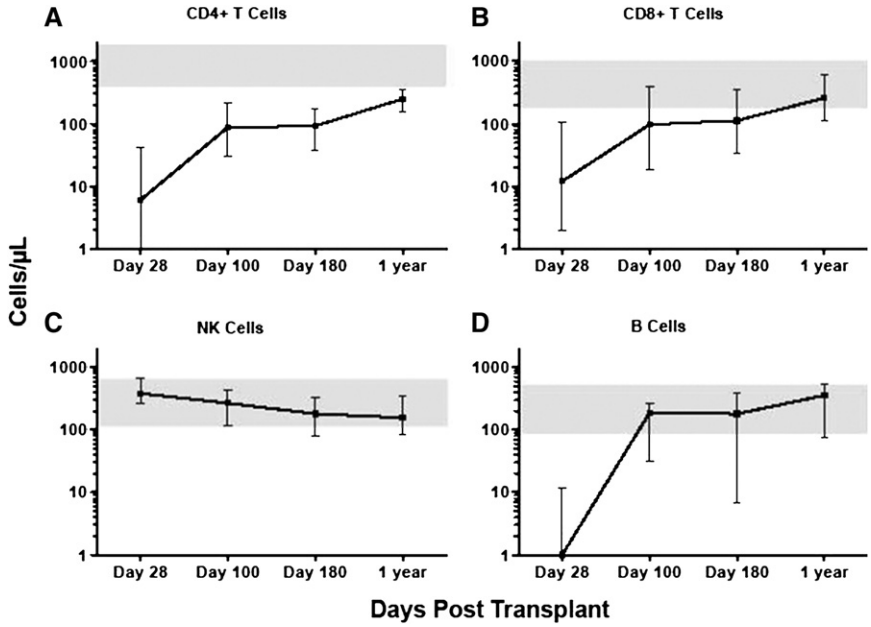

Figure 1. Recovery of lymphocytes by day posttransplantation. Values are expressed as median ± standard error. Shaded areas represent the 25th-75th percentile range for normal individuals. (A) $CD4^+$ cells. (B) $CD8^+$ cells. (C) NK cells ($CD56^+$ cells). (D) B cells.

were able to achieve the target CD34 dose of 5.0×10^6/kg. This resulted in a primary engraftment rate of 100%. One patient experienced secondary graft failure despite receiving an initial CD34 dose of 10.1×10^6 $CD34^+$ cells/kg. The pathophysiology of secondary graft failure is complex, and multiple factors may contribute to this event. Overall, the risk of primary or secondary graft failure was very low in this trial, supporting our choice of target CD34 cell dose.

The incidence of severe or life-threatening conditioning regimen–related toxicity was relatively low in this trial, suggesting that the regimen was generally well tolerated despite the median patient age of 48.5 years. The most common early toxicity was mucositis. The most serious toxicity was pulmonary-related, typically occurring between 30-100 days post-HCT. Within the first 100 days after HCT, 14% of the patients experienced grade 3-5 pulmonary toxicity, possibly attributed to the conditioning regimen. Idiopathic pneumonia syndrome is a well-described regimen-related toxicity associated with various high-dose conditioning regimens [29]. Overall, the rate of pulmonary complications observed in this trial was similar to or lower than the rates reported in previous trials in which myeloablative conditioning was used [30,31]. Interestingly, 1 study found an association between TCD and a lower risk of pulmonary complications compared with standard GVHD prophylaxis [31].

The rates of bacterial, fungal, and CMV infections encountered in the present trial did not appear to be any greater than those reported after conventional PBSC transplantation [1,32]. The low rates of acute and chronic GVHD and the absence of immunosuppressive drugs also may play roles in limiting opportunistic infections [33]. One exception is the risk of EBV reactivation, which is increased in recipients of T cell–depleted

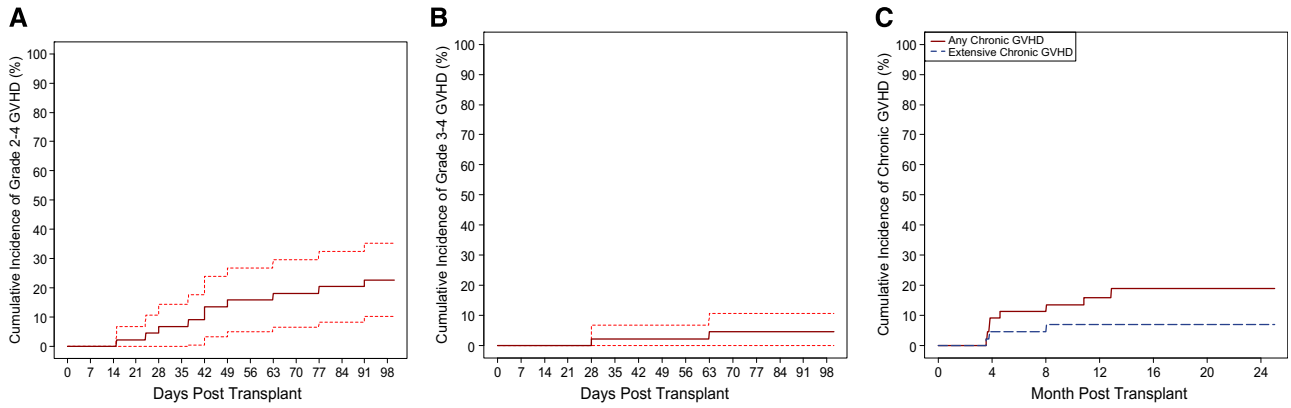

Figure 2. Cumulative incidence of grade II-IV acute GVHD (A), grade III-IV acute GVHD (B), and extensive/limited chronic GVHD (C).

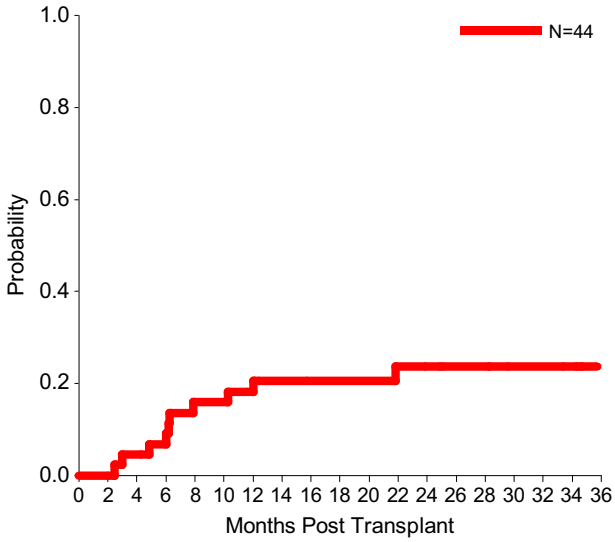

Figure 3. Cumulative incidence of relapse for all transplant recipients.

transplants [34]. Eight patients (18%) developed evidence of EBV viremia requiring at least 1 dose of rituximab, and 1 patient died from PTLD. Thus, close monitoring for EBV infection is imperative at least up to day +100 in recipients of $CD34^{+}$-enriched allografts, because early treatment with rituximab may be able to reverse this condition in a high proportion of cases.

Relapse remains the major cause of death in patients receiving allografts for high-risk AML [1,2,4,5,35]. Because CD34 enrichment results in a TCD of 4-5 logs, there is a concern that it might decrease the putative graft-versus-leukemia effect [36]. Although this has been demonstrated clearly in patients with chronic myelogenous leukemia, there is no convincing evidence of higher relapse rates after TCD HCT for AML in remission [10,36-38]. The cumulative incidence of relapse in CR1 of <20% at 3 years suggests either the retention of a graft-versus-leukemia effect or, alternatively, the highly effective antileukemic nature of the conditioning regimen used. It is more difficult to comment on the observed risk of relapse in patients with AML in CR2, because of our low patient numbers. Only 7 patients in this trial underwent HCT while in CR2, 4 of whom relapsed. These results are in contrast to previous reports suggesting favorable outcomes after TCD HCT for AML patients in CR2 [13,14,39]. We cannot draw any definitive conclusions for this group at this time; further investigation is needed to define the relapse risk for this population.

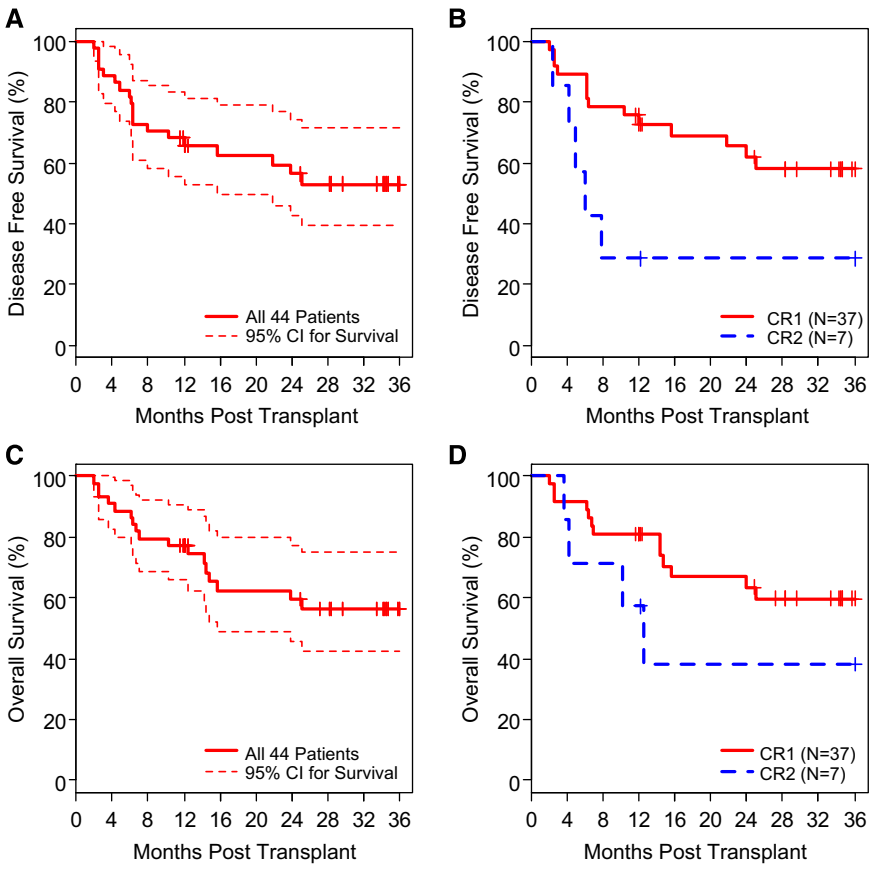

Figure 4. Kaplan-Meier estimates of DFS for all transplant recipients (A), DFS by remission state (B), OS for all transplant recipients (C), and OS by remission state (D).

Although the transplantation of PBSCs may mitigate complications early after HCT, late complications related to chronic GVHD appear to be more common. A recent meta-analysis of 9 randomized trials comparing PBSCs and bone marrow clearly demonstrated a higher risk of extensive chronic GVHD after transplantation of HLA-matched sibling mobilized PBSCs [8]. The chronic GVHD observed after PBSC HCT may be more difficult to treat and may require a greater duration of corticosteroid use compared with that seen in bone marrow HCT, resulting in a higher risk of late complications [6,40]. In this context, the very low risk of extensive chronic GVHD observed in the present trial suggests another potential advantage of this approach. The low risk of both relapse and chronic GVHD makes this approach attractive for selected high-risk patients with AML in remission.

In conclusion, this study demonstrates that TCD HCT after intensive myeloablative chemoradiotherapy conditioning can be performed successfully in a multicenter setting using a single TCD method without additional posttransplantation pharmacologic GVHD prophylaxis. The low incidences of relapse and of acute and chronic GVHD in the absence of posttransplantation prophylaxis are especially encouraging. A second study to confirm these findings in unrelated donor HCT is currently being planned by the Blood and Marrow Transplant Clinical Trials Network.

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