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T-CELL DEPLETED UNRELATED DONOR STEM CELL TRANSPLANTATION PROVIDES FAVORABLE DISEASE-FREE SURVIVAL FOR ADULTS WITH HEMATOLOGIC MALIGNANCIES

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Abstract

We report a prospective phase II clinical trial in 35 adult patients (median age 40.5 years) with hematologic malignancies who received T-cell depleted, hematopoietic stem cell transplants from HLA-compatible, unrelated donors. The cytoreductive regimen consisted of hyperfractionated total body irradiation, thiotepa, and fludarabine. The preferred graft source was G-CSF-mobilized peripheral blood stem cells (PBSC). PBSC were CD34+ selected, followed by sheep erythrocyte rosetting to deplete residual T cells. Antithymocyte globulin provided graft rejection prophylaxis. No additional graft versus host disease (GvHD) prophylaxis was planned. Estimated disease free survival at 4 years is 56.8% for the entire group and 75% in patients with standard risk disease. The cumulative incidence of relapse is 6%. Acute GvHD grade II-III developed in 9% and chronic GvHD in 29% of patients. Fatal infections occurred in 5 of 35 (14%) patients. There was one late graft failure. This study demonstrates durable engraftment with a low overall incidence of GvHD. Its curative potential is reflected in the remarkably low relapse rate at 4 years.

INTRODUCTION

Several studies have demonstrated the efficacy of TCD allogeneic bone marrow (BM)[1–3] and TCD peripheral blood stem cell transplants (PBSCT)[4,5] from matched related donors (MRD) in patients with hematologic malignancies. In these reports, reduction in the

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incidence and severity of acute and chronic GVHD, compared with T-cell replete transplantation, has not compromised the anti-tumor effect of the allograft. Furthermore, a 5 year followup of patients receiving TCD sibling transplants reported excellent performance status and quality of life.6 In contrast, TCD transplants from unrelated donors have been less well studied.3,7,8

Although the addition of antithymocyte globulin (ATG) addressed an early unacceptable rate of immune-mediated graft rejection and provided additional GVHD prophylaxis beyond that of TCD alone 9,10, it has resulted in delayed immune recovery.11 We reported recently that conditioning with hyperfractionated total body irradiation (HFTBI), thiotepa, and fludarabine in TCD PBSCT using MRD eliminated the need for ATG without increasing graft rejections. Furthermore, immune reconstitution improved with a reduction in opportunistic infections (OI).5

In order to extend curative transplantation options to patients without a MRD and to an older population at increased risk of GVHD, we utilized this regimen for matched or mismatched unrelated donor transplants. Only 2 doses of ATG were administered and TCD was performed by automated CD34+ stem cell selection followed by rosetting with sheep red blood cells (sRBC). We report the results of a trial in 35 patients which evaluated the impact of this approach on transplant related morbidity and mortality in patients with hematologic malignancies .Secondary endpoints were to estimate disease-free and overall survival. We sought also to determine if patients could achieve consistent engraftment with durable relapse-free survival and whether T-cell reconstitution could be improved with a low incidence of OIs.

MATERIALS and METHODS

Patient characteristics

Thirty-five adult patients with a variety of malignant hematologic diseases and treatment backgrounds were enrolled on this MSKCC Institutional Review and Privacy Board-approved phase II trial from July 1, 2001, to December 31, 2005, after obtaining informed consent. Analysis was performed as of December 31, 2008, after which there were no censored events. Eligibility included low level of disease or remission, availability of ≥7/10 HLA matched, unrelated donor, Karnofsky performance status (KPS) ≥70; no active infection or extramedullary disease, and satisfactory organ function as previously described. 5

Only those patients with intermediate or high risk AML based on cytogenetics 12, and with ALL high risk cytogenetics [generally t(9;22) with p190 *bcr-abl* or t(4;11)] underwent transplantation in CR1. Disease status at transplant determined standard or poor risk classification: AML-CR1, -CR2, ALL-CR1, or CML-first chronic phase were standard risk, all others were poor risk.5 HLA matching for -A, -B, -C, -DRB1, and -DQB1 loci was established using DNA sequence-specific oligonucleotide probes. Donors were identified and recruited via the National Marrow Donor Program (NMDP) registry.

Preparative regimen and graft

The cytoreduction consisted of HFTBI followed by thiotepa, ATG, and fludarabine5. HFTBI was administered in 11 fractions of 125 cGy over 4 days, to a total dose of 1,375 cGy. All patients had protective lung shielding after an initial 800cGy, and overlying ribs received an additional 600 cGy boost. Male patients with acute leukemia or lymphoma received an additional 400 cGy testicular boost in a single fraction After completion of HFTBI, thiotepa 5 mg/kg/day was administered over 4 hours on each of 2 consecutive days, with no adjustment for weight. Fludarabine 25 mg/m^2/day was administered over 30 minutes

for 5 days, beginning on the first day of thiotepa. Patients received 2 doses of equine (60 mg/kg total) or rabbit (5 mg/kg total) ATG divided over the same 2 days as the thiotepa. The source of rabbit ATG was Sangstat until 2003 and there after Genzyme.

Twenty-nine donors underwent G-CSF mobilization of PBSC according to NMDP guidelines. Targeted cell dose was 10^9 MNC/kg (3×10^6 CD34+/kg) of recipient weight. CD34+ cells were positively selected using the ISOLEX 300i Magnetic Cell Selection System, followed by sRBC-rosette depletion of T cells 5. This achieved an approximate 5 $\log_{10}$ depletion of CD3+ cells. 13 Six donors elected BM harvesting with TCD accomplished by sequential soybean lectin agglutination and sRBC -rosette depletion (SBA-E-) 14. Fresh grafts were infused through a central venous catheter 24-48 hours after completing fludarabine.

GVHD evaluation and management

GVHD was diagnosed clinically and confirmed by biopsy whenever possible. , Patients, who engrafted and survived >30 days, were evaluable for acute GVHD, unless it had already been diagnosed before a terminal event. Scoring was based on CIBMTR criteria15. Patients surviving >100 days were evaluable for chronic GVHD using the Sullivan scoring criteria. 16

Supportive care

Patients were managed clinically according to MSKCC standard guidelines 5 including infection prophylaxis for *Pneumocystis carinii*, Herpes viruses, and fungus. Patients who were seropositive for *Toxoplasma gondii* or whose donors were seropositive, also received atovaquone prophylaxis after transplantation. Patients who were cytomegalovirus (CMV) negative received seronegative blood products regardless of the donor's serologic status. If the patient or donor was seropositive, CMV-specific prophylaxis was administered beginning when the absolute neutrophil count (ANC) was self-sustaining > 2000 cells/ul and continuing through d+100. This consisted of maintenance dosing of valganciclovir as peripheral blood counts tolerated and maintenance foscarnet dosing if they did not. Monitoring of CMV reactivation by CMV pp65 antigenemia assay of peripheral blood was performed regularly when either the patient or donor was CMV seropositive, generally once per week during the first 100 days. Epstein-Barr virus (EBV) was monitored similarly by qualitative PCR until 2003 and thereafter by real-time PCR of the BNRF1-p143 locus (Roche Inc) 17.

Prophylactic antibacterial agents were not used until 2005. At that time, the practice of administering vancomycin prophylaxis against Streptococcus viridans at the development of neutropenia or no later than d -2 was initiated. This practice affected 4 patients on this study. Finally patients received G-CSF beginning ≥ d+7, if clinically indicated.

Engraftment, donor chimerism, and immune reconstitution

Standard engraftment criteria were used ANC ≥500/uL without G-CSF support and platelets ≥20,000/uL without transfusion for ≥3 consecutive days. BM aspirates were monitored for disease status and donor chimerism.

Immunophenotyping and T cell proliferative responses to phytohemagglutinin (PHA) mitogen were evaluated every 3-6 months until normal.18 Life-threatening infections were defined as organ-localized infections due to viral, fungal, and/or parasitic pathogens as previously described.5

Biostatistics

Disease free survival (DFS), defined as the interval from transplantation to death, hematological or clinical relapse, or last follow-up, was estimated using the method of Kaplan-Meier. Estimates of the probability of relapse and non-relapse mortality (NRM) were calculated with the cumulative incidence function.19 Wilcoxon rank sum test was used to compare immune reconstitution results between groups of patients. Primary cause of death was determined by previously published criteria20.

RESULTS

Patient and donor characteristics

Table 1 details patient and donor characteristics. Median patient age was 40.5 years, with 10 patients ≥50 years. Eighteen patients were classified as standard risk and 17 were poor risk. Two BM grafts arrived in poor condition and could only be processed with soybean agglutination. This necessitated short term calcineurin inhibitor therapy with these grafts which contained 2.3 and 2.6 × 10^6CD3+/kg (1-2 logs higher than the CD3+ dose in other grafts). Eighteen donors were HLA disparate at 1-3 of 10 loci (Table 1). Four patients received 2 doses of rabbit ATG by physician choice. Two patients received 1 dose of rabbit and 1 dose of horse ATG due to a reaction during the first dose.

Engraftment and donor chimerism

All 34 evaluable patients engrafted neutrophils. One infectious death on day +5 was inevaluable. CD34+ and CD3+ cell dose engraftment data are summarized in Table 2. The median CD34+ dose was within the range targeted by the protocol (3 × 10^6 CD34+cells/kg). Ten grafts contained less than the targeted dose, half were the TCD BMs. The patient who received the lowest CD34+ dose (TCDBM, 0.8 × 10^6/kg) exhibited delayed engraftment and required a BM boost. Three of 34 evaluable patients died before achieving platelets >20,000/ul.

One patient with ALL CR2 rejected a 9/10 HLA matched PBSCT. Day +30 evaluation revealed only 55% donor chimerism with multiple new chromosomal abnormalities. This pt died from complications following a second transplant. Thirty of the 34 evaluable patients achieved full donor chimerism in BM by d+100. Four were not evaluated.

At 1 year, 21 of 26 evaluable patients were studied: 19 had full donor chimerism, 2 were ≥ 80% donor. One improved with an infusion of donor lymphocytes (DLI), the other spontaneously. Within 24 months posttransplantation (the last evaluation required by protocol), 21 of 25 evaluable patients studied demonstrated ≥95% donor chimerism. The 1 patient with an HLA matched donor who received low dose DLI for mixed chimerism did not develop GVHD.

GVHD

The median CD3+dose for the 35 patients was 1.52 × 10^3 CD3+ cells/kg, far below the threshold of 1 × 10^5 CD3+cells/kg for developing acute GVHD determined by limiting dilution outgrowth using TCD BM from HLA-identical siblings 21. Thirty-four of the 35 patients were evaluable for acute GVHD (Table 2). The incidence of grade II-IV was 5.8%. One of these patients, with an HLA-matched donor, received the highest T cell dose (22.8 × 10^3CD3+/kg) among the TCD PBSC grafts. The second patient received a mismatched BM allograft containing 15.7 × 10^3CD3+/kg. Their grade IV lower GI GVHD responded quickly to steroid therapy.

Twenty-eight patients were evaluable for chronic GVHD. Five developed limited and 3 extensive. Three previously had acute GVHD. Incidence was similar in those with matched (18%) vs. mismatched (11%) donors (7-8/10 matches). One patient required calcineurin inhibitor prophylaxis because of the higher residual T cell content in the graft. Three patients died from complications of chronic GVHD. The overall incidence of chronic GVHD was 29%, with only 11% extensive.

DFS and relapse

Patients had a variety of diagnoses and treatment histories, and were almost equally divided between 'standard' (n=18) and 'poor' (n=17) risk disease (Table 1). Estimated probabilities of DFS and overall survival (OS) at 4 years for the entire group were 57% and 59%, respectively (median followup 52 months). Figure 1 illustrates the probability of DFS at 4 years for patients following standard risk - 75%, compared to poor risk transplants – 41% (p=0.057). Figure 2 illustrates OS. DFS and OS for patients ≥ 40 years were not significantly different from that for younger patients. Ten patients were ≥50 years, 4 in the poor and 6 in the standard risk transplant groups. Three of the 10 died from early infections (adenovirus, toxoplasma, and VRE sepsis), 1 each from chronic GVHD, interstitial pneumonitis, and an unrelated gastrointestinal malignancy (at 72 months). No significant difference was observed for matched vs mismatched transplants in DFS and OS showed borderline significance (p=0.54), however, the number of patients is limited.

Cumulative incidence of relapse at 4 years is only 6% (Figure 3 (A)). Both patients who relapsed had poor risk disease: 1 with acute biphenotypic leukemia, who developed leukemia cutis during conditioning, relapsed at 38 months; the second with ALL CR2 relapsed at 31 months Both received second (T-replete) transplants and 1 survives in remission at 30 months.

Of the 18 patients who were HLA-mismatched, 4 donor-recipient pairs exhibited KIR ligand incompatibility. Of these, 3 pairs had KIR ligand incompatibility in a host-versus-graft vector, and only one pair had KIR ligand incompatibility in a graft-versus-host vector. For this one pair, however, donor KIR genotyping revealed lack of the relevant inhibitory KIR responsible for sensing the class I ligand lacking in the recipient. . All of the remaining HLA-mismatched patients were KIR ligand compatible.

Posttransplantation EBV-LPD

Three patients (8.5%) developed biopsy-confirmed EBV-LPD, at 3, 6, and 7 months. All recovered with therapy (1 rituximab, 1 rituximab + DLI, 1 EBV-specific cytotoxic T cells). The patient who received DLI from their C allele mismatched donor at 3 months eventually died from complications of GVHD. Death was attributed to complications of EBV-LPD.

Causes of death

Fourteen (40%) of the 35 patients died by the 4 year followup. Five had matched and 9 had mismatched donors. Causes of death are summarized in Table 2. Cause-specific probability of NRM, adjusted for the competing risk of relapse, is 20% at 100 days, and 29% at 1 year (Figure 3(B)).

Immune reconstitution and infections

The median time to recovery of normal numbers of circulating CD8+ T cells and to >200 CD4+ T cells/uL was 4-6 and 6-9 months, respectively (Figure 4). Only 4 patients who received steroids within the first 12 months had persistently low CD4+ cells (<100 cells/uL) throughout the first 2 years. By 12-18 months, CD4+CD45RA+ cells recovered in 50% of patients, and the majority of patients' PHA T cell proliferative responses reached the lower

limit of normal (LLN). All patients developed normal numbers of CD56+CD16+ NK cells by 2 months after transplant (data not shown).

The 30 day absolute lymphocyte count (ALC), reported to predict outcomes in TCD HLA-matched sibling transplant patients with acute leukemia or CML22, was analyzed for the entire group. Median ALC at 30 days was 474 cells/uL. There was no difference in the incidence of death or relapse for patients with an ALC at 30 days above or below this median (data not shown). Thirty patients, who achieved a circulating lymphocyte count of 500 cells/uL, did so at a median time (range) of 19.5 (14 to 223) days.

Eleven of 35 patients developed a life-threatening OI due to adenovirus (n=5), EBV (n=3), fungus (n=1), toxoplasmosis (n=1), or Nocardia (n=1). Three of 16 patients at risk for CMV reactivation required treatment: 1 CMV colitis and 2 viremias. Three additional patients experienced nonfatal RSV infections and 1 atypical mycobacterium infection Five died of their OIs: 2 adenovirus, 1 each toxoplasmosis, EBV, and fungus. Four of these patients had received mismatched grafts.

DISCUSSION

This trial addresses the use of myeloablative TCD transplantation from HLA matched and mismatched unrelated donors with current day technology and practices. The goals were to provide effective therapy with a low rate of relapse, to facilitate T cell recovery, and to decrease regimen related toxicity. Despite the high risk nature of many of the transplants and modifications to the regimens, the study demonstrated promising results: only a 6% cumulative incidence of relapse, excellent engraftment, and low rates of GVHD. Confounding contributors to GVHD were incomplete TCD and use of DLI. Death due to infection occurred in 20% of patients, most in the peritransplant setting or in association with GVHD therapy.

Limited reports of TCD unrelated BM or PBSC grafts following myeloablation have been published7‚23-26 Most studies utilized partial TCD together with immune suppressive medications25 post transplant. They reported slower immune recovery, a higher incidence of infectious complications, 18‚27‚28 and relapse in certain diseases compared with T-cell replete transplantation 29-31. Use of ATG has also been associated with similar complications. 1‚32 The majority of studies, including the largest trial 33, described patients treated in the 1980's-2000 using BM allografts. The current study addresses an older patient population, but incorporates improved supportive care, high resolution HLA typing, improved TCD technology, and PBSC graft source.

Studies suggest that higher doses of CD34+ cells facilitate engraftment and immune reconstitution.34-36 In this study, TCD PBSCs grafts had 5.75 $\times 10^6$/kg median CD34+ cell doses, similar to T-cell replete PBSC37, and much higher than 1.2 $\times$ 10^6/kg for TCD BM grafts (historical, unpublished results) . Log 10 depletion of CD3+ in PBSC was 5.5 compared with 2.5-3 for BM. The level of TCD in this study is approximately 1/2 log greater than that achieved with the currently available CliniMACS device 38.

Median age of the patients was >10 years older than our earlier reports and similar to our recent study of TCD matched, related PBSC transplants.1‚2‚5 Distribution of diseases was representative of older patients and included many treated at advanced stages. Infectious complications reflect current day pathogens but notably, did not include *Streptococcal* bacteremias which were observed with this regimen previously5. Early initiation of antibiotics, for fevers during conditioning, may have avoided this complication.

This trial evaluated changes in the regimen and graft. Despite reducing the intensity of the conditioning, the OS and DFS for the 17 'standard' risk patients was excellent, >70% and comparable to our previous results5 and those reported by others. The Kaplan-Meier survival curve for this group did not change after the 8^{th} month. The OS and DFS for the 'poor' risk transplant group was 47% and 41%, respectively, again similar to those with T-cell replete grafts, but with less GVHD. Median follow up for this trial was >4 years, encompassing the only 2 relapses. The very low incidence of relapse argues against a loss of graft versus tumor effect with TCD. Deaths on this trial generally occurred within the first 6-8 months and were predominantly infection-related.

The low relapse rate in the setting of a TCD allograft invokes the possibility that NK cells are the primary mediator of the graft-versus-tumor effect. Classic NK alloreactivity due to killer Ig-like receptor (KIR)-mediated recognition of "missing self" occurs when MHC class I KIR ligands present in donor are lacking in the transplant recipient. Only 4 of the 18 HLA-mismatched donor-recipient pairs exhibited KIR ligand incompatibility and only 1 of these pairs had KIR ligand incompatibility in a graft-versus-host vector. For this 1 pair, however, donor KIR genotyping revealed lack of the relevant inhibitory KIR responsible for sensing the class I ligand lacking in the recipient; and thus, no NK alloreactivity due to recognition of missing self would occur. Donor NK alloreactivity due to missing self-MHC, therefore, could not account for the low relapse rate among these patients.

NK alloreactivity due to "missing ligand," which we have previously described39, can occur when the patient is lacking any class I ligand for donor inhibitory KIR, irrespective of whether the ligand is present in the donor. This receptor-ligand mismatch occurred in 22 of the 35 pairs. Because the event of relapse is low in this small cohort, however, we cannot conclude that NK alloreactivity due to missing ligand is responsible for protection from relapse. A larger cohort would be necessary to confirm this.

A goal of the current study was to reduce the dosing of ATG and potentially improve immune recovery without increasing the incidence of graft rejection or GVHD. Based on previously identified predictors of graft rejection using TCD BM grafts9,40, more than half the patients were at increased risk. However, only 1 HLA mismatched graft recipient, in the poor risk group, experienced late graft failure. Enhanced immunosuppression provided by fludarabine coupled with the higher CD34+ dose achieved with PBSCs likely contributed to the high rate of durable engraftment. These results support further reduction in ATG dosing in future trials.

The TCD PBSC contained >1 $\log_{10}$ lower concentration of T cells compared with TCD BM grafts (median 1.2 vs 42.5×10^3/kg)14 and a 4 $\log_{10}$ lower concentration than T-cell replete PBSC grafts with similar CD34+ numbers . 37 However, the incidence and severity of GVHD in this study, is higher than that previously reported for our TCD BM and PBSC with matched related donors2,5, and for HLA haplotype disparate related donors reported by Aversa et al. 41 Factors contributing to the GVHD might include: 1) additional allogeneic disparities in unrelated and mismatched donors; 2) qualitatively different T cell and NK populations in TCD PBSC vs. TCD BM; and 3) the relatively low dose of ATG employed.

The goal of utilizing lower dose ATG was to improve T cell recovery and potentially reduce life-threatening OIs. Recovery of CD4 counts to ≥200 and normalization of CD8 T cells were similar for the TCD PBSC (6-9 months), compared with unrelated TCD BM (12-18 months) 18. CD4+CD45RA+ cell recovery was also faster than for unrelated TCD BM. Thus, despite including ATG, time to recovery of CD4+ and CD4+CD45RA+cell counts in this trial was similar to that for recipients of related TCD PBSC using identical cytoreduction but without ATG.5 Similarly, patients' PHA response normalized faster on

this trial than in recipients of TCD unrelated BM, who had a PHA response <25% LLN for the first year vs the median PHA response in this study of 60% LLN at 12 months, and normal by 18 months. Keever-Taylor et al. recently published the results of lymphoid recovery in patients transplanted on the National Heart, Lung and Blood Institute randomized TCD versus T-cell replete unrelated BM trial which included posttransplant immunosuppression.42 Despite the older age of the current study patients, recovery of CD4+ cells was similar and CD4+ CD45RA+ cells more rapid compared to that reported by Keever-Taylor et al. (median age 31.2 years).

Infection as the primary cause of death occurred in 17%. This is lower than the 29 and 30% incidence of fatal infection reported by Wagner et al. in recipients of T-cell replete or TCD unrelated stem cell transplants who received immunosuppressives for GVHD prophylaxis. 43 Furthermore, the higher incidence of deaths from CMV and fungus reported by van Burik et al. in TCD unrelated transplant recipients who also received posttransplant GVHD prophylaxis44 was not observed in this study. No patient died of CMV disease and only 1died of a fungal infection.

This study supports the use of TCD PBSC transplantation from both matched and mismatched unrelated donors in appropriately selected adult patients, especially those at increased risk of GVHD. Acknowledging the limited numbers of patients, the median survivals compare favorably with those reported by the NMDP for each disease group45. The risk of relapse was remarkably low, with a median followup of >4 years. The character of complications and death were similar to those observed with T-replete transplantation, but with a lower incidence and severity of GVHD. Adequately TCD PBSC from unrelated donors precludes the need for posttransplant GVHD prophylaxis, allowing more rapid recovery of functional immunity that reduces the risk of lethal opportunistic infections. It provides an alternative form of transplantation for patients without sibling donors including those who are older than 40 years.

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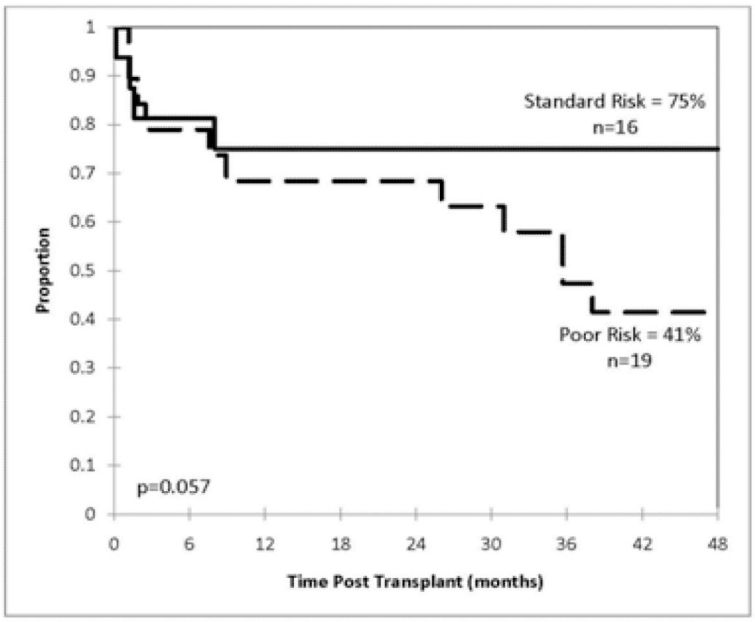

Figure 1.
Kaplan-Meier estimates of the probability of disease free survival at 4 years based on the status of disease.

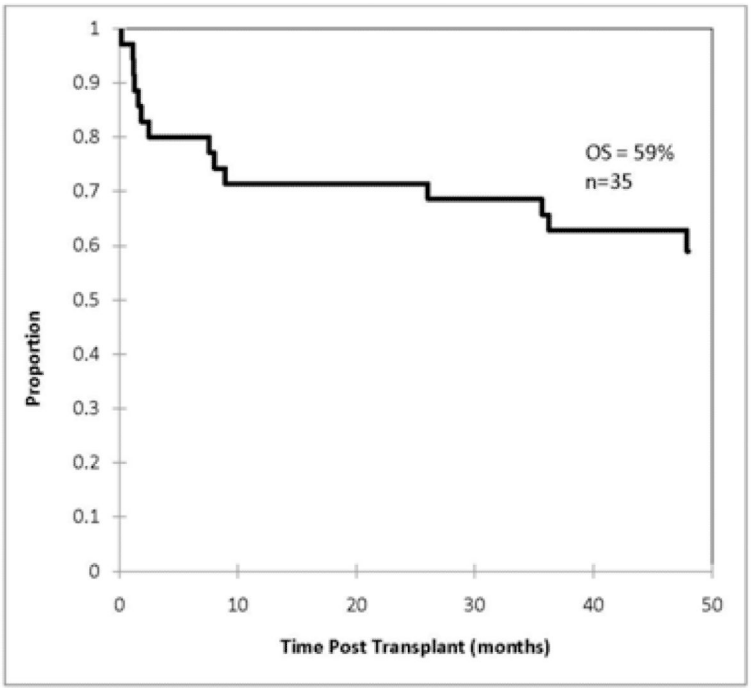

Figure 2.
Kaplan-Meier estimates of the probability of overall survival at 4 years for all patients.

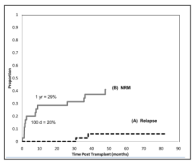

Figure 3.
Cause specific analysis of relapse and mortality. (A) cause specific probability of relapse, adjusting for completing risks of treatment failure by nonrelapse causes (B) cause specific probability of death, adjusting for the competing risk of relapse.

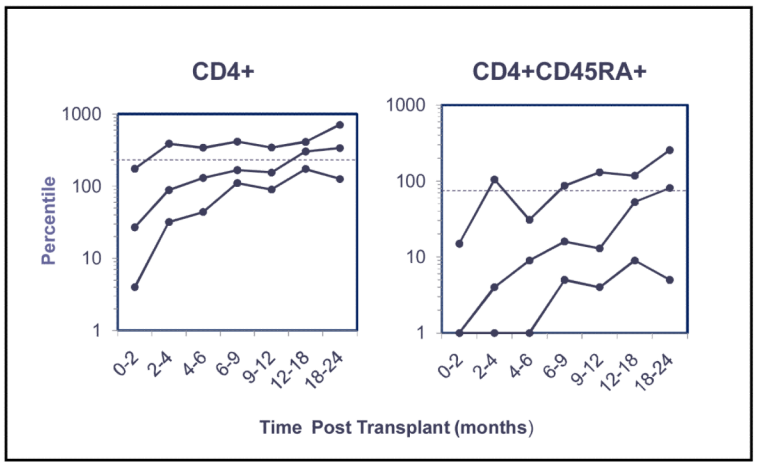

Figure 4.
T cell recovery. Shown are the 10-50-90th percentiles of CD4+ and CD45RA+ cells per microliter obtained over 24 months for 26 patients following peripheral blood stem cell transplantation on this study.

TABLE 1

PRETRANSPLANT DEMOGRAPHICS AND DISEASE STATUS

Total # Pts	**35**
KPS – range (median)	**70-100 (90)**
M:F	**21-14**
Age – range (median)	**18.2-62.8 (40.5)yr**
Diseases	
AML CR1	6
Intermediate Risk*	3
High Risk	3
AML CR2	10 (1 after MDS)
ALL CR1	3
ALL CR2	7
ALL CR≥3	3
AL (other)	2 (1 CR, 1 extramedullary relapse)
CML CP1	1
MDS	2 (1 RA- Intermed IPSS, I RAEB)
T-PLL	1
Donors	
Matched: Mismatched	17:18
M → F	9
M → M	12
F → M	7
F→ F	7
Age – range (median)	**19-54 (36) yr**
Grafts	
PBSC	29
BM	6
HLA Disparity for MM Transplants	**18**
9/10 1 antigen A;C	2;2
1 allele A;C;DQ	2;1;1
8/10 2 antigen A,C;A,DQ;B,C	1;1;2
1 antigen+1 allele A,DQ;A,C;	1;2
C,DR;DR,DQ	1;1
7/10 1 antigen+2 alleles	
A,C,DQ	1

AML indicates acute myelogenous leukemia; ALL, acute lymphocytic leukemia; AL, acute leukemia multilineage; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; RA, refractory anemia; RAEB-IT, refractory anemia with excess blasts in transformation; T-PLL, T cell prolymphocytic leukemia; CP, chronic phase; CR, complete remission;

*by cytogenetics; KPS, Karnofsky performance status.

TABLE 2

OUTCOME DATA

Median Follow-up (range)	**52 (37-83.1)mns**
Engraftment	**34 (evaluable)**
Median transplant dose CD34+×10^6/kg (range)	3.9 (0.80-11.57)
Median transplant dose CD3+×10^3/kg (range)	1.52 (0-259)
Patients engrafting neutrophils	34
Median days to ANC ≥ 500/uL (range)	12 (9-19) days
Patients engrafting platelets	32
Median days to platelets ≥ 20,000/uL (range)	19 (14-108) days
Post Transplant EBV-LPD	**3**
GVHD	
Acute (overall grade)	2/34 (1M:1MM)
II	1 (1M)
IV	1 (1MM)
Chronic	8/28 (5M:3MM)
Limited	5 (2M: 3MM)
Extensive	3 (3M)
Relapses	**2**
ABL > CR2 (w/extramedullary disease)	1
ALL CR2	1
Deaths	**14**
Matched: Mismatched	6 : 8
Causes of Death	
Infection	6
Bacterial	2
Viral (adenovirus)	2
Toxo/fungal	1/1
EBV-LPD and secondary complications	1
Post 2nd transplant complications	1
GVHD and secondary complications	3
Late GF	1
IP	1
VOD	1
100 day NRM	**20% (2M : 5MM)**
Bacterial	l
Viral (adenovirus)	2
Toxo: bacterial	1 : 2
VOD	1
Late GF	1

Mns indicates months; ul, microliter; EBV-LPD, Epstein Barr virus-lymphoproliferative disease; M, matched; MM, mismatched; ABL, acute biphenotypic leukemia; ALL, acute lymphocytic leukemia; CR, complete remission; GVHD, graft versus host disease; toxo, toxoplasmosis; GF, graft failure; IP, interstitial pneumonitis; VOD, venoocclusive disease.