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Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation for Patients with Hematologic Malignancies Who Relapse following Autologous Transplantation: A Multi-Institutional Prospective Study from the Cancer and Leukemia Group B (CALGB trial 100002)

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Abstract

We prospectively treated 80 patients with relapse of malignancy or secondary myelodysplasia after autologous hematopoietic cell transplantation (AHCT) with allogeneic hematopoietic cell transplantation (allo-HCT) using a reduced-intensity conditioning (RIC) regimen of fludarabine 150 mg/m2 plus intravenous busulfan 6.4 mg/kg. Both sibling (MSD) and unrelated donors (MUD) were allowed. Patients transplanted from MUD donors received more intensive graft-versus-host disease (GVHD) prophylaxis, including rabbit anti-thymocyte globulin 10 mg/kg,

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mycophenolate mofetil, and an extended schedule of tacrolimus. With a median follow-up of 3.1 years (0.9 to 5.8), TRM at 6 months and 2 years was 8% and 23% respectively. Neither TRM nor the rates of acute GVHD were different in those with sibling or MUD donors. Donor CD3 cell chimerism > 90% at day +30 was achieved more often in patients with MUD than with MSD donors, 70% versus 23% ($p<0.0001$). Median EFS was higher in patients who achieved early full donor chimerism (14.2 versus 8 mo, $p = 0.0395$). Allo-HCT using this RIC regimen can be performed with low TRM in patients who have received a prior AHCT. Efforts to improve early donor CD3 chimerism may improve EFS.

Introduction

High-dose chemotherapy with autologous hematopoietic cell transplantation (AHCT) is a curative therapy for several hematologic malignancies. However, relapse of malignancy (RM) or the development of secondary myelodysplasia (MDS) and acute myeloid leukemia (AML) are important causes of treatment failure following AHCT. Allogeneic hematopoietic cell transplantation (allo-HCT) can cure some patients who develop RM or MDS/AML following AHCT[1-7]. However, the use of traditional myeloablative allo-HCT for this purpose has been associated with high rates of treatment-related mortality (TRM) which has limited its use[3-5,7]. Studies of reduced-intensity conditioning (RIC) allo-HCT from selected groups have suggested that such transplants may be associated with lower and more acceptable rates of TRM when used following AHCT[8-10]. However, it has not been demonstrated that low TRM can be achieved in the context of a multi-institutional national cooperative group. We hypothesized that RIC allo-HCT would produce a low TRM following failure of AHCT in the context of a cooperative group. We also hypothesized that the use of a more aggressive regimen for the prophylaxis of graft-versus-host disease (GVHD) in patients with matched unrelated donors (MUD) would result in a similar low rate of TRM in these patients when compared to patients with HLA-identical matched sibling donors (MSD). Cancer and Leukemia Group B (CALGB) study 100002 tested these hypotheses and the results of this trial are reported here.

Patients and Methods

The study was performed prospectively at approved allogeneic transplant centers of the Cancer and Leukemia Group B (CALGB).

Eligibility

Patients were required to have developed recurrence of malignancy or secondary MDS/AML > 6 months following AHCT for a hematologic malignancy. Other eligibility criteria included: age < 70 years, HIV-negative, non-pregnant and non-nursing, satisfactory vital organ function (LVEF ≥ 30%, DLCO >40% predicted, creatinine clearance ≥ 40 ml/min, bilirubin/AST ≤ 3 × upper limit of normal). Patients were required to have either an HLA-identical sibling donor (MSD) or a 10/10 [HLA A, B, C, DRB1 and DQB1] allele matched unrelated donor (MUD). Patients provided informed consent and the study was approved by the Cancer Treatment Evaluation Program (CTEP) of the National Cancer Institute and the Institutional Review Board (IRB) of each participating center

Treatment Regimen

The preparative regimen consisted of fludarabine 30 mg/m2/day i.v. × 5 days (day -7 through -3) and busulfan 0.8 mg/kg q 6 hours i.v. × 2 days (day -4, -3). MUD patients also received rabbit antithymocyte globulin (ATG) (Thymoglobulin®; Genzyme, Cambridge, MA) at a dose of 2.5 mg/kg/d × 4 days (d -4 through -1). G-CSF mobilized donor peripheral blood hematopoietic cells (CD34+ cell dose 2-8 × 10^6/kg) were infused on day 0. G-CSF 5

μg/kg/d was administered from d +7 until the absolute neutrophil count (ANC) recovered to ≥ 1000/mcl. GVHD prophylaxis consisted of tacrolimus twice daily (starting d -1 to maintain levels at 5-10 ng/mL and then tapered as tolerated starting d +90 for MSD patients and d +180 for MUD patients) and methotrexate 5 mg/m2 i.v. (d +1, +3, and +6 for MSD patients and d +1, +3, +6 and +11 for MUD patients). Patients with MUD also received mycophenylate mofetil 15 mg/kg p.o. twice daily from d -2 through d +60.

Supportive care recommendations included acyclovir 200-400 mg three times daily, cotrimoxazole twice weekly and fluconazole (200-400mg/d) or voriconazole 200-300 mg twice daily and weekly CMV monitoring with pre-emptive therapy through d +100 (or longer in patients with active GVHD)

Donor lymphocyte infusions (DLI) were allowed only for persistent or progressive malignancy. Patients receiving DLI were required to have no active GVHD and to have ceased immunosuppressive therapy for > 30 days. MSD patients received escalating dose DLI at 8 week intervals according to the following schedule − 1×10^7, 5×10^7, 5×10^7 CD3+ cells/kg. MUD patients received the following doses also at 8 week intervals: 5×10^6, 1×10^7, 5×10^7 CD3+ cell/kg

Evaluations

Patients were evaluated for toxicity and GVHD twice weekly through d +28, weekly through d +100 and monthly through d +365. Restaging of malignancy was performed every 3 months through 3 years post allo-HT and every 6 months thereafter. Centralized chimerism studies were performed at the HLA laboratory at University of California, San Francisco by Dr Lee-Ann Baxter-Lowe. Chimerism was analyzed separately in peripheral blood T-cells, and myeloid-origin cells using a PCR-based method that routinely achieved 1% sensitivity. CD3 and CD14/15 cells were selected from peripheral blood mononuclear cells (Ficoll-Hypaque fraction) using Miltenyi magnetic particles (Miltenyi Biotec, Bergisch Gladbach, Germany). The purity of each cell subset was determined by flow cytometry. Two short tandem repeat (STR) loci were amplified for each donor-recipient pair (selected from VWF, D21S11, D18S51, D16S539, PENTA D, D3S1358, FGA, D7S820, D2S1338, D10S2325, D12S391, SE33, PENTA E). Amplicons were separated using an automated nucleotide sequencer (ABI 3100 Applied Biosystems, Foster City, CA, USA) and the quantity of each informative allele from duplicate samples was determined using GeneMapper fragment analysis software (Applied Biosystems, Foster City, CA, USA). Every assay included sensitivity controls (mixtures of donor and recipient DNA) and if preferential amplification was observed, a standard curve was also included to normalize the data [11]. Full-donor chimerism was defined as > 90% of cells being of donor origin at the time point tested (d+30, +60, +90 and +180).

Statistical Considerations

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians. The study was designed as a phase II trial with a sample size of eighty patients to assess the null hypothesis that treatment-related mortality (TRM) at 6 months post allo-HCT would exceed 25%. TRM was defined as death from any cause in the absence of disease progression/ relapse. A four-stage design was utilized with stopping rules based upon the number of patients who experience TRM at each stage. The study was designed so as to have a power of 0.92 at the one-sided 0.08 level. TRM was calculated according to the cumulative incidence method. Relapse was treated as a competing risk. Descriptive statistics were used to determine patient characteristics. Time-to-event distributions were estimated using the

Kaplan-Meier method. Overall Survival was determined from the date of allo-HCT, while Event-Free Survival was defined as time to death or progression of malignancy. Time-to-event distributions were compared using the log-rank test. Fisher's exact test was used to compare the rate of complications between MSD and Mud patients.

Audit Information

As part of the quality assurance program of the CALGB, members of the Audit Committee visit all participating institutions at least once every three years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 22 patients (27%) of the 82 patients under this study.

Results

Patient Characteristics

Eighty-two patients were registered on this study from eleven CALGB allogeneic transplant centers. Two patients were withdrawn between registration and initiation of study treatment and eighty patients were treated on this study. Their characteristics are shown in Table 1. Median follow-up from the date of registration on study is 3.1 years (range 0.9-5.8 years).

Treatment Related Mortality, Overall and Event-Free Survival

All living patients had greater than 6 months follow-up from allo-HCT at the time of analysis. Seven of 80 patients died of TRM within 6 months (8.8%). The estimated cumulative probabilities (with 95% confidence intervals) of TRM for all patients at six months and two years were 8% (2-14%) and 23% (14-32%) respectively (Fig. 1A). The corresponding estimated cumulative probabilities of TRM (with 95% confidence intervals) for the MSD and MUD patients were 3% (0-8%), 12%(0-24%) respectively at 6 months, and 28% (13-43%), 19% (7-31%) respectively at 2 years (p=NS) (Fig 1B).

Reported causes of death were: infection 6, GVHD 6, pneumonitis/respiratory failure 4, coagulopathy 1, renal failure 1, cerebral ischemia 1, post-transplant lymphoproliferative disease 1.

The estimated probability of overall survival at 6 months and 2 years was 84% (95% CI 74%-90%) and 47% (36%-58%) respectively (Fig 2A). Event-free survival at 6 months and 2 years was 62% (51%-72%) and 29% (20%-40%) respectively (Fig 2C). Neither median survival (1.93 years vs. 1.69 yrs) nor median event-free survival (0.96 vs. 0.54 years) were significantly different for MSD and MUD patients (Figs 2B, 2D).

GVHD and Infections

The cumulative incidence of acute and chronic GVHD is shown in Fig 3. The cumulative incidence of acute GVHD at one year was 44% (95% CI 33-55%). It was not significantly different between MSD and MUD patients - 55% (35-67%) versus 37% (25-52%) respectively. The corresponding cumulative incidence of severe (grade 3 and 4) acute GVHD at one year was 15% (7-23%) for all patients and 22% (9-35%) versus 9% (0-18%) respectively for MSD and MUD patient (p=NS). The cumulative incidence of chronic GVHD at two years was 45% (34-56%) for all patients and was significantly higher for MSD versus MUD patients - 59% (43-75%) versus 33% (19-47%) (p=0.015). The corresponding cumulative incidence of extensive chronic GVHD in all patients at two years was 23% (14-32%) in all patients and was significantly higher in MSD versus MUD patients - 36% (20-52%) versus 12% (2-22%) respectively (p=0.009).

The cumulative incidence of reported viral, bacterial and fungal infections was not statistically different between MSD and MUD patients (65% versus 74%).

Chimerism

Chimerism was separately analyzed for T-cells (CD3+) and cells of myeloid origin (CD14/15+) in the peripheral blood at monthly time points following transplantation. The results of CD3 chimerism are shown in Table 2. Patients transplanted from a MSD were significantly less likely to achieve full donor CD3+ cell chimerism than MUD patients at d +30 and d +90 ($p<0.0001$ and $p=0.017$ respectively). However there was no significant difference at later time points. Full-donor chimerism in peripheral blood myeloid cells (CD14/15+) was achieved in 94% of MSD patients and 97% of MUD patients on d +30 and by 94% of both groups by d +90. Patients who achieved full donor CD3 chimerism at d +30 post allo-HCT had a significantly better EFS ($p=0.0395$, log-rank test) than patients who failed to achieve full donor CD3 chimerism by this time-point (median EFS 14.2 months versus 8 months, EFS at 2 yrs 38% versus 23%, Fig. 4). The corresponding values for median OS were 36 months versus 15.6 months respectively (p=NS).

Donor Lymphocyte Infusions

Nine patients received a total of 18 DLI for progression/persistence of malignancy. Two patients (HD, CLL) responded by achieving a CR after one and three DLI that remains durable at the time of reporting. Seven patients (2 HD, 5 MM) showed no response or progressive malignancy following DLI.

Discussion

This study assessed the tolerability of reduced-intensity conditioning allo-HCT to treat RM or MDS/AML developing after AHCT for hematologic malignancies. Although patients with RM following AHCT may theoretically face a different risk of recurrent malignancy following allo-HCT than patients with MDS/AML following AHCT, they face similar questions regarding the tolerability of allo-HCT following a prior AHCT. They were therefore included in this study. Consistent with our hypothesis, the estimated probability of TRM was only 8% at 6 months and 23% at 24 months. While there was a suggestion of a higher TRM in MUD patients at 6 months (estimated cumulative probability 12% versus 3%, p=NS) the TRM at 2 years was not different between the donor types. These data suggest that the use of reduced-intensity conditioning can abrogate the high TRM traditionally seen when myeloablative allo-HCT was used following failure of AHCT. Furthermore, our data suggest that low TRM can be achieved within the context of a multi-institutional co-operative group trial. Whereas it is likely that the reduced-intensity of the preparative regimen is the predominant cause of the low TRM seen, advances in supportive care that have occurred since the originally reported studies of allo-HCT following failure of AHCT may also have contributed. In support of this suggestion, a recent retrospective analysis of myeloablative allo-HCT as second transplant for lymphoma performed by the Center for International Blood and Marrow Transplant Research (CIBMTR) demonstrated a three-year TRM of only 22% [12].

We also hypothesized that the use of a more aggressive GVHD prophylaxis regimen in patients receiving transplants from MUD would eliminate the greater risk of acute and chronic GVHD traditionally reported for MUD transplants versus transplants from MSD. In order to test this hypothesis we used only fully matched unrelated donors (10 of 10 match at HLA - A, B, C, DRB1 and DQ alleles), and HLA-identical sibling donors in this study. As expected, the incidence and severity of GVHD was not greater in MUD transplant patients in our study. Indeed the incidence and severity of chronic GVHD was lower in MUD

patients than in MSD patients. In this respect our GVHD prophylaxis regimen for MUD patients may have been overly aggressive. All MUD donors used were fully matched. Several reports published since the inception of our study have shown that there appears to no increased incidence of GVHD or mortality in patients receiving allele-matched MUD transplants when compared to those transplanted from MSD even when similar GVHD prophylaxis is used for the two groups[13-15]. Indeed, the higher risk of GVHD and mortality seen in older comparisons of MUD versus MSD donor transplants may be related to allele-level HLA-incompatibility between MUD and recipient that was undetected by the serological and low-resolution typing used in those studies[16].

Chimerism was studied separately for peripheral blood T-cells and myeloid cells. This analysis revealed that the RIC regimen used here (fludarabine and low dose busulfan) results in full-donor chimerism in myeloid cells at all time points following transplant in both MSD and MUD patients. However, in the MSD patients (in whom ATG was not used in the preparative regimen) relatively few patients achieved CD3+ cell full-donor chimerism (23% by d +30). CD3+ chimerism improved at later time points following transplant such that by d +120 and +180 62% and 81% of MSD patients achieved full-donor CD3+ cell chimerism. As DLI were not allowed for low level CD3+ chimerism in the absence of malignant progression in this study, the lack of early full-donor CD3+ cell chimerism may have limited the graft-versus-malignancy effect in these patients. On the other hand, it may have had a protective effect against acute GVHD. Other investigators have reported a delay in achievement of full donor T-cell chimerism when using busulfan based reduced-intensity regimens[17-19]. Some reports have associated the failure to achieve full-donor T-cell chimerism at d +30 with < 2 prior chemotherapy regimens before allo-HCT[17,19]. This pattern was seen in our study despite the fact that all patients had > 2 prior chemotherapy regimens as well as a prior AHCT. The rate of early full-donor T-cell chimerism was also unrelated to the interval between prior AHCT and the allo-HCT (data not shown). The use of ATG in the preparative regimen may be at least partly responsible for the much higher rates of full-donor T-cell chimerism for MUD patients in our study. The ability of ATG to augment the rates of donor T-cell chimerism seen early post allo-HCT has been previously described[20]. The impact of delayed early T-cell chimerism seen in the MSD patients in our study is unclear. Some investigators have associated such a delay with an increased rate of relapse of malignancy [18,19] although others have not found such an effect[17]. We showed a significantly favorable effect of full-donor T-cell chimerism at d +30 on EFS in this study.

Although TRM was low as hypothesized in our study, long-term EFS was disappointing (29% for both MSD and MUD patients at 2 years). At the time of reporting, sixteen of the eighty patients transplanted on this study are alive and free of malignancy. it is possible that many of these patients may be cured. However, measures to lower the rate of early relapse seen are clearly necessary when designing follow-up studies in this population. Options include the addition of low dose ATG to improve early T-cell chimerism in the MSD patients, targeting a higher pharmacokinetically directed dose of busulfan in the preparative regimen, reduced post-transplant GVHD prophylaxis and maintenance anti-cancer therapy in the post-transplant period.

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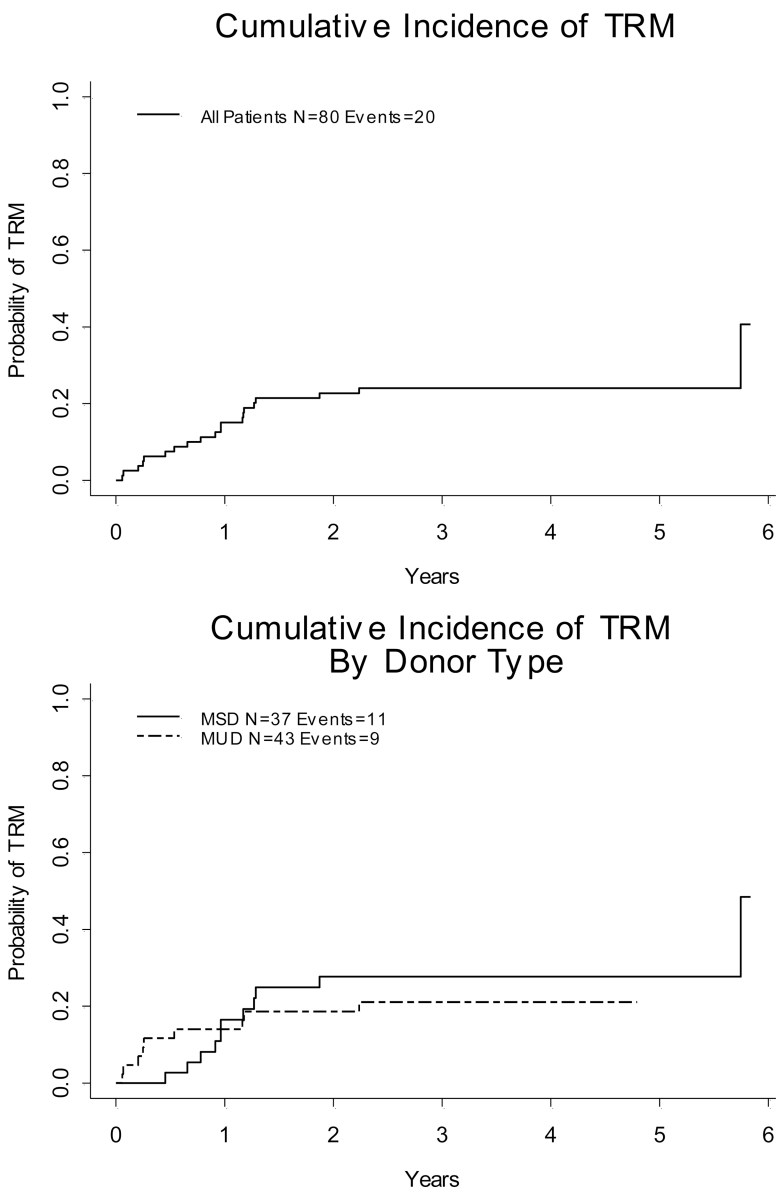
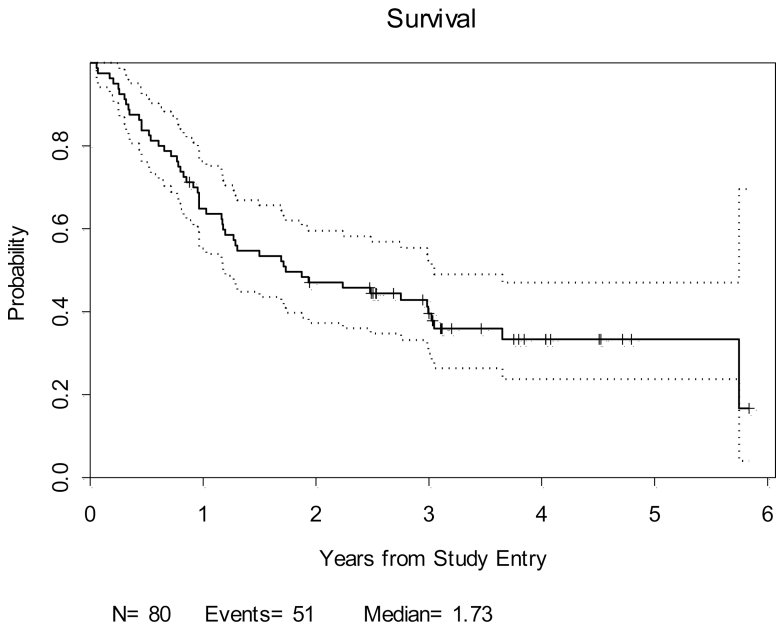
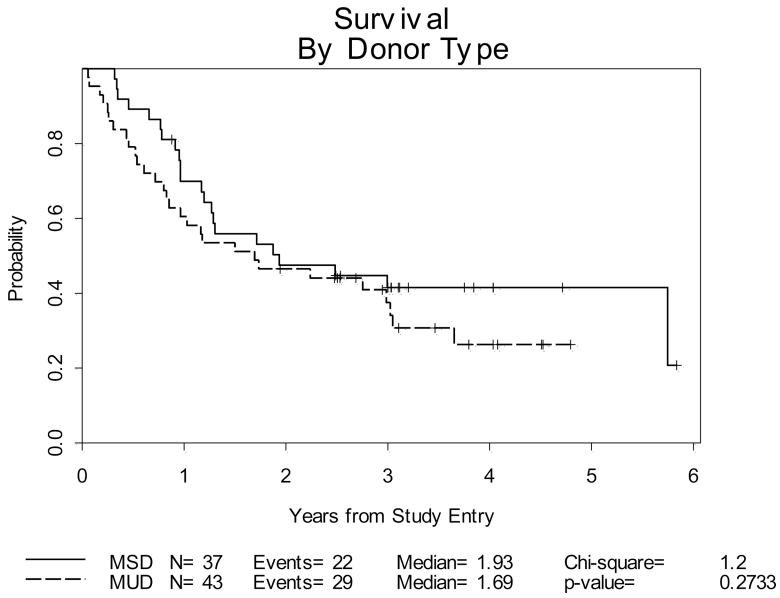


Fig. 1. Treatment Related Mortality

The cumulative estimated probability and 95% confidence intervals of treatment related mortality is shown. (A) All patients. (B) TRM for HLA-identical sibling donor patients and matched-unrelated donor patients.





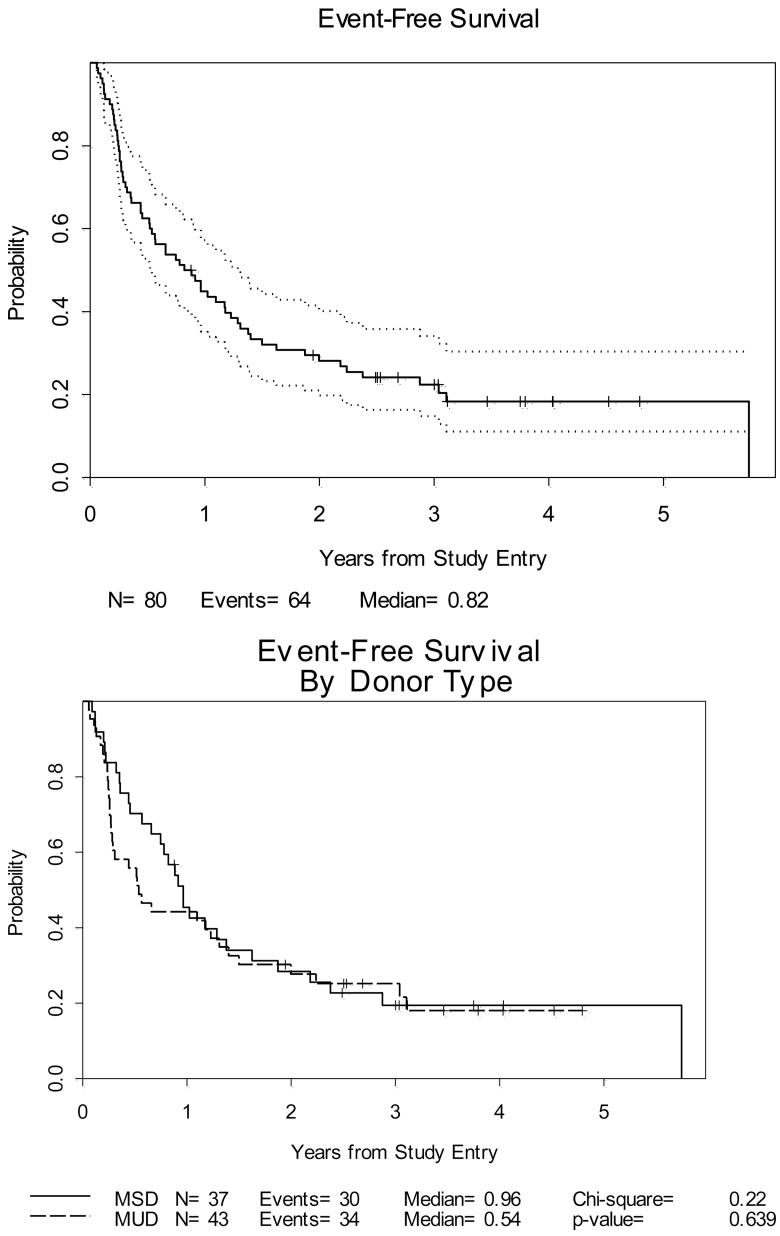
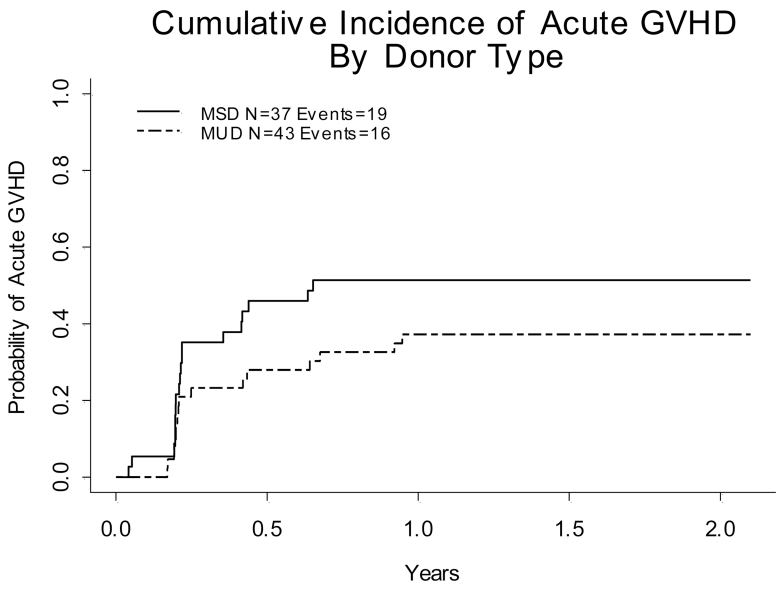
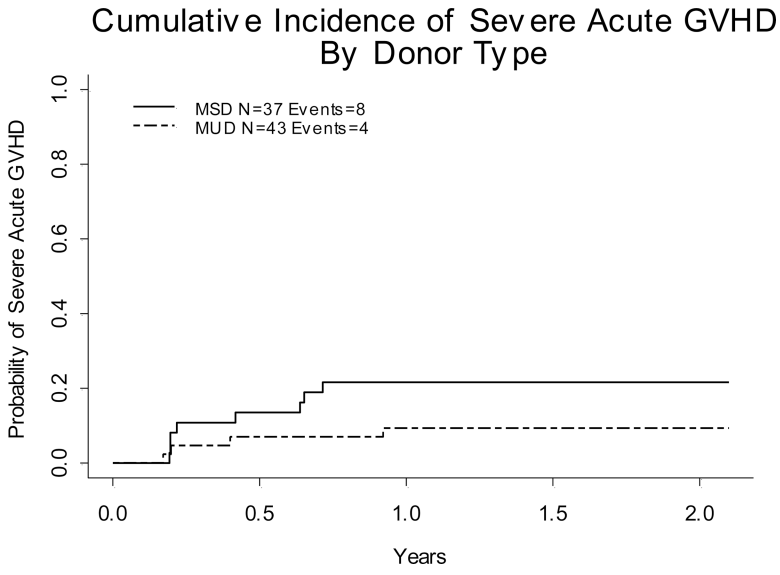


Fig. 2. Overall and Event-Free Survival

The estimated probability of Overall Survival (A, B) and Event-Free Survival (C, D) is shown. Probabilities shown are for all patients (A, C) and by donor type (B, D)





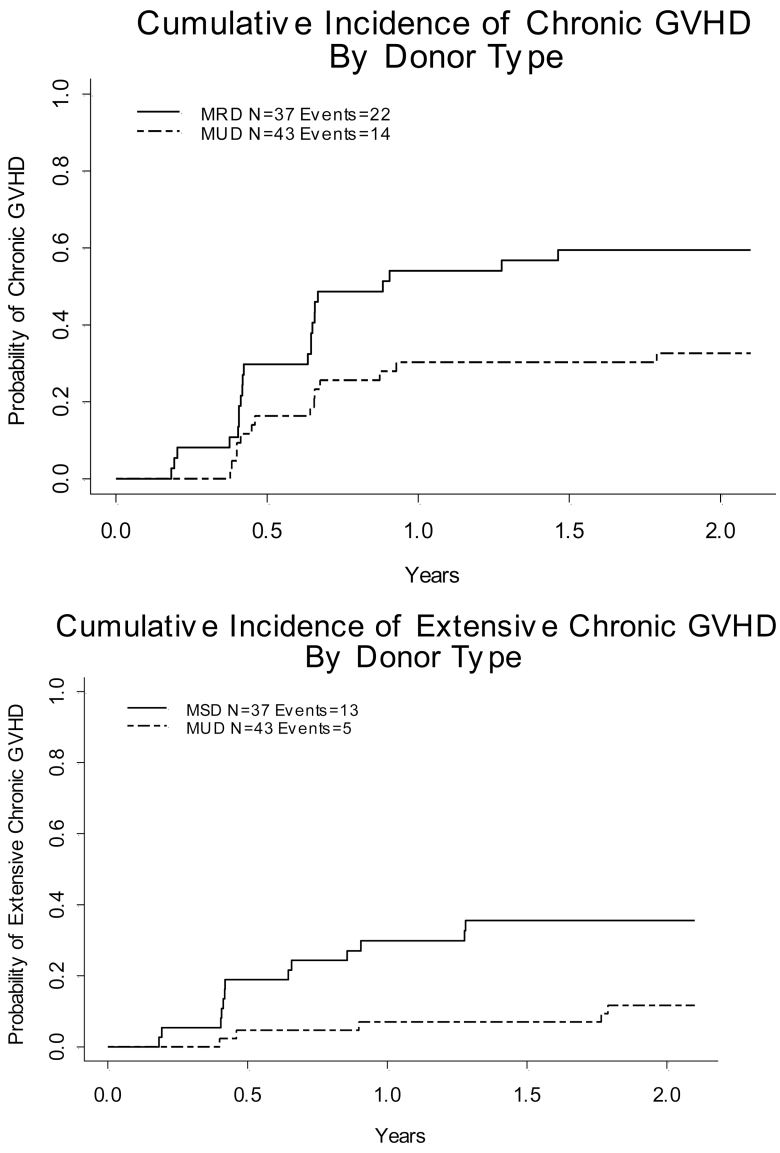


Fig. 3. GVHD

The cumulative incidence of acute and chronic GVHD by donor type is shown. (A) Acute GVHD, (B) Severe – (grade 3 & 4) acute GVHD, (C) Chronic GVHD, (D) Extensive stage chronic GVHD

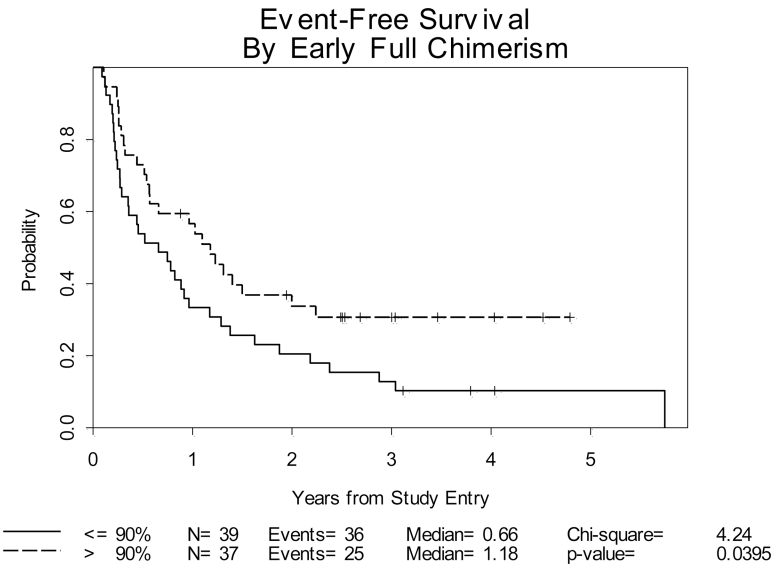


Fig. 4. Effect of CD3 Chimerism on Event-Free Survival

Event-Free Survival is shown for patients who achieved > 90% donor-derived CD3+ cells in peripheral blood by day +30 (dashed line) versus patients who achieved ≤ 90% donor-derived CD3+ cells (solid line)

Table 1

Patient Characteristics

	Donor Type					
	MSD (n=37)		MUD (n=43)		All (n=80)	
Characteristic	n	%	n	%	n	%
Race						
White	30	81.1	43	100.0	73	91.2
Hispanic	2	5.4	0	0.0	2	2.5
Black	3	8.1	0	0.0	3	3.8
Asian	2	5.4	0	0.0	2	2.5
Male	26	70.3	23	53.5	49	61.2
Diagnosis						
NHL	15	40.5	11	25.6	26	32.5
HD	8	21.6	9	20.9	17	21.2
MM	6	16.2	10	23.3	16	20.0
CLL	0	0.0	1	2.3	1	1.2
de novo AML	4	10.8	4	9.3	8	10.0
de novo MDS	0	0.0	1	2.3	1	1.2
Therapy related AML/MDS	4	10.8	7	16.3	11	13.8
Age						
Median, range	51	24-70	48	17-67	51	17-70
Years from prior transplant						
Median, range	2.1	0.6-17.3	2.7	0.6-6.8	2.4	0.6-17.3

MSD = HLA-identical sibling donor, MUD = matched unrelated donor

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Table 2

CD3 Chimerism

	MSD	MUD	Total
Day 30			
≤ 90%	27 (75.0%)	12 (30.0%)	39 (51.3%)
> 90%	9 (23.1%)	28 (70.0%)	37 (48.7%)
Total	36	40	76
p-value			< 0.0001
Day 60			
≤ 90%	20 (55.6%)	12 (33.3%)	32 (44.4%)
> 90%	16 (44.4%)	24 (66.7%)	40 (55.6%)
Total	36	36	72
p-value			0.0962
Day 90			
≤ 90%	16 (50.0%)	6 (18.8%)	22 (34.4%)
> 90%	16 (50.0%)	26 (81.2%)	42 (65.6%)
Total	32	32	64
p-value			0.0169
Day 120			
≤ 90%	11 (37.9%)	4 (16.0%)	15 (27.8%)
> 90%	18 (62.1%)	21 (84.0%)	39 (72.2%)
Total	29	25	54
p-value			0.13
Day 180			
≤ 90%	4 (18.2%)	2 (4.8%)	6 (14.3%)
> 90%	18 (81.2%)	18 (90.0%)	36 (85.7%)
Total	22	20	42
p-value			0.26

The number and percentage (in parenthesis) of patients who achieved > 90% donor-derived versus ≤90% donor-derived CD3+ cells in peripheral blood is shown at time points from day 30 through day 180 following transplant. MSD = HLA identical sibling donor patients. MUD = matched unrelated donor patients