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Allogeneic stem cell transplantation for advanced myelodysplastic syndrome: Comparison of outcomes between CD34+ selected or unmodified hematopoietic stem cells transplants

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Abstract

Purpose—To compare transplant outcomes in patients with advanced myelodysplastic syndrome (MDS) after CD34+ selected or unmodified allografts.

Patients and Methods—This analysis included initially 181 patients; 60 underwent CD34+ selected transplant and 121 had an unmodified transplant. Due to significant differences in disease

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characteristics, the analysis was limited to patients who had <10% blasts prior to transplant (N=145). Two groups were defined: (1) low risk: good and intermediate risk cytogenetics ($CD34^+$, N=39; unmodified, N=46), and (2) high risk: poor and very poor risk cytogenetic ($CD34^+$, N=19; unmodified, N=41).

Results—In the low risk group, grade II-IV acute GVHD at 1 year was 18% in the $CD34^+$ subgroup vs. 41.3% in the unmodified subgroup, p=0.015. There were no differences in the incidence of grade III-IV acute GVHD. Chronic GVHD at 3 years was 5.3% vs. 56%, p<0.001, respectively. At 3 years, relapse, overall survival (OS) and relapse-free survival (RFS) for the $CD34^+$ and unmodified subgroups were similar: 8.1% vs 19.4%, p=0.187; 58.5% vs 53.7%, p=0.51; 59.5% vs 52.4%, p=0.448. However, the composite outcome combining chronic extensive GVHD free status and relapse free status (CRFS) at 3 years was 59.5% in the CD34+ selected group vs 19.2% in the unmodified group, p<0.001.

In the high risk group, $CD34^+$ vs. unmodified, grade II-IV acute GVHD at 1 year was 31.6% vs 24.4%, p=0.752. There were no differences in the incidence of grade III-IV acute GVHD. Chronic GVHD at 3 years was 0% vs. 27.6%, p=0.013. At 3 years, relapse, OS, RFS, and CRFS were 31.6% vs. 69.3%, p=0.007; 35.5% vs 14.5%, p=0.068; 31.6% vs 10.7% p=0.045; and 31.6% vs 6.1%, p=0.001, respectively. Cytogenetic abnormalities at diagnosis and transplant type had a significant univariate association with RFS in the high-risk cohort. Only cytogenetics (p=0.03) remained associated with this outcome in a multivariate model.

Conclusions—Overall survival was similar between the two types of transplant, however CRFS was superior in $CD34^+$ selected transplants.

Keywords

myelodysplastic syndrome; allogeneic transplantation; T cell depletion; unmodified

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment available for patients with myelodysplastic syndrome (MDS)[1,2]. Despite major improvements in transplant outcomes, mostly due to decrease in transplant related mortality (TRM) [3, 4, 5], graft versus host disease (GVHD) and relapse remain the major challenges affecting quality of life and survival post-transplant.

Acute and chronic GVHD are significant post-transplant complications with cumulative incidence ranging from 30 to 60%[6,7]. A very effective method to prevent GVHD is depletion of T lymphocytes from the allograft before infusion [8,9, 10, 11, 12, 13, 14,15]. Although several different methods were used in the past to deplete T cells ex-vivo [16,17,18] more recently the only method available is positive selection of $CD34^+$ stem cells. The efficacy of ex-vivo $CD34^+$ selection in reducing the risk of acute and chronic GVHD without higher relapse rates has been reported in previous publications[19, 12,14]. These findings were confirmed in a prospective multicenter phase 2 trial sponsored by the Bone Marrow Transplant Clinical Trial Network in patients with acute myeloid leukemia in complete hematologic remission 7. To date, results from prospective trials comparing $CD34^+$ selected to unmodified transplants have not been reported. However, retrospective comparison studies have been published in

patients with acute myelogenous leukemia (AML) in first complete remission[20] and acute lymphoblastic leukemia (ALL)[21] in first or second complete remission and have shown similar survival although with much less GVHD in the $CD34^+$ selected transplants. This study compares the standard transplant outcomes and also the composite end point of chronic GVHD free and relapse free survival (CRFS)[22] which is currently being studied in a prospective manner through a BMT CTN study (BMT CTN 1301, NCT02345850) in patients with advanced MDS who underwent $CD34^+$ selected allo-HSCT at MSKCC with those who received unmodified allo-HSCT at MDACC between 2001–2012.

Patients and Methods

Patients

Adult patients (18 and older) who underwent allo-HSCT for advanced MDS (RAEB-1&2), between 2001 and 2012 were included in this retrospective analysis after approval by each institutional Review Board. Demographics, disease characteristics, treatment, GVHD and survival data were retrieved from databases at the respective institutions. The MDS subtypes and prognostic classification at diagnosis and before transplantation were determined according to the 2008 World Health Organization (WHO)[23] and the Revised International Prognostic Scoring (IPSS-R) criteria[24]. Donor-recipient human leukocyte antigen (HLA) matching was established by DNA sequence-specific oligonucleotide typing for HLA-A,-B,-Cw,-DQB1, and –DRB1 loci, in both institutions.

Transplant Procedure and Supportive Care

Sixty patients who received $CD34^+$ selected grafts at MSKCC and 121 patients who received unmodified grafts at MDACC were identified initially for this retrospective analysis. All recipients of $CD34^+$ selected grafts underwent myeloablative conditioning regimen (MAC): 55 (92%) had a chemotherapy-based regimen and 5 (8%) had a TBI-based regimen. T cell depletion of granulocyte colony-stimulated factor (G-CSF) -mobilized PBSCs was accomplished by positive selection of $CD34^+$ stem cells using the ISOLEX 300i Magnetic Cell Separator (Baxter, Deerfield, IL) and then sheep RBC rosette depletion (N= 30)[25], and since October 2010 the CliniMACS CD34 Reagent System (N=25)[26] (Miltenyi Biotech, Gladbach, Germany). Five patients received bone marrow (BM) graft wherein T cell depletion was achieved by sequential soybean lectin agglutination and sRBC-rosetting[11, 14], which provides level of T cell depletion similar to $CD34^+$ selection. The T cell depleted allograft was infused within 24–48 hours after completion of cytoreduction. All patients received antithymocyte globulin (ATG) to prevent graft rejection. No pharmacologic post transplant GVHD prophylaxis was given.

Of the 121 patients who received unmodified graft at MDACC, 81 (67%) after a MAC and 40 (33%) after a reduced intensity conditioning regimen (RIC). All patients received a chemotherapy based regimen; the backbone for the MAC regimen was a combination of busulfan and fludarabine (91.3%) and the backbone of the RIC regimen was melphalan and fludarabine (65%). The GVHD prophylaxis consisted of tacrolimus and mini-dose methotrexate (5 mg/m^2 on days 1, 3, 6 and 11) in the majority of patients (N=118). ATG was

given to all recipients of matched unrelated donor (MUD) (N=59). Patients were managed at both institutions according to each institution's standard guidelines.

GVHD was diagnosed clinically, confirmed pathologically whenever possible, and classified according to standard criteria for acute GVHD [27] and for chronic GVHD[28]. Only patients who engrafted were evaluable for GVHD assessment. Cause of death was determined using a NMDP algorithm[29]. CRFS was defined as the combined outcome of being alive and free of chronic extensive GVHD and relapse state[22].

Statistical methods

Patient characteristics were compared between $CD34^+$ selected and unmodified transplant groups using the Wilcoxon Rank-Sum test for continuous covariates and Chi-square or Fisher's exact test for categorical covariates as appropriate. OS and RFS were defined as the time from transplant until death, and relapse or death, respectively. CRFS was defined as the time from transplant until death, relapse, or extensive cGVHD. Estimates and 95% confidence intervals for OS, RFS, and CRFS were calculated using the Kaplan-Meier method, with comparisons across groups based on the log-rank test. The cumulative incidence of relapse, non-relapse mortality, aGVHD, and cGVHD were estimated using the cumulative incidence method for competing risks, with differences across groups based on Gray's test. Death in the absence of relapse was considered a competing risk for relapse, while relapse was considered a competing risk for non-relapse mortality. For acute and chronic GVHD, death and relapse were both considered to be competing risks. Cox proportional hazards regression was used to investigate the joint effects of patient characteristics on RFS in multivariate analysis.

Results

Patient Characteristics

Patient demographics and clinical characteristics of all patients in both groups are summarized in table 1. Patients in the unmodified cohort had higher proportion of therapy-related MDS (31.4% vs. 11.7%, p=0.007), very poor risk cytogenetics at diagnosis (34.7% vs. 13.6%, overall p=0.016) and BM blast count >10% at time of transplant (24.3% vs. 0%, overall p<0.001). The $CD34^+$ selected cohort had a higher number of patients receiving PB grafts (91.7% vs. 67.8%, p=0.001), HLA-mismatched donors (N = 14, 23.3%), and all patients were conditioned with a myeloablative regimen. The median (range) time from diagnosis to transplant was 8.2 (1.8, 161.1) months in the $CD34^+$ selected cohort and 7.4 (0.9, 53.0) months in the unmodified cohort (p=0.314).

Considering the significant differences between the 2 cohorts, patients with ≥ 10% blasts at the time of transplant were excluded and the analysis was limited to two groups that had similar characteristics: (1) Low risk group: patients with <10% blasts at time of transplant and good and intermediate risk cytogenetics at diagnosis ($CD34^+$ selected, N=39, unmodified, N=46). (2) High risk group: patients with <10% blasts at time of transplant and poor and very poor risk cytogenetics at diagnosis ($CD34^+$ selected, N=19, unmodified,

N=41). The patient's characteristics of these two groups are summarized in table 2 and all comparison results are summarized in table 3.

The median follow-up among survivors in the low risk $CD34^+$ selected and unmodified subgroups was 43.4 months (range: 3.8–109.2) and 44.9 months (range: 12.9–115.6). In the high risk $CD34^+$ selected subgroup, the follow-up was 52 months (16.2–119.5) and 53.3 months (14.2–93.9) in the unmodified subgroup.

Acute graft-versus-host disease

In the low risk group, the day-100 cumulative incidence (CI) of grade II-IV aGVHD was 12.8% (95% CI 4.6–25.4%) in the $CD34^+$ selected subgroup and 41.3% (26.9–55.1%) in the unmodified subgroup. The 1-year CI of grade II-IV aGVHD was 18.0% (7.8–31.7%) and 41.3 % (26.9–55.1%), respectively (p=0.015). Grade III-IV aGVHD was 12.8% (4.6–25.4%) in the $CD34^+$ selected subgroup and 13.0% (5.2–24.5%) in the unmodified subgroup at day 100 and 15.4% (6.1–28.5%) and 15.2% (6.6%−27.1%) at 1 year post-transplant (p=0.98).

In the high-risk group, the day-100 CI of grade II-IV aGVHD was 15.8% (3.7–35.6%) in the $CD34^+$ selected subgroup and 22% (10.7–35.7%) in the unmodified subgroup. At 1-year, it was 31.6% (12.3–53%) and 24.4% (12.5–38.4%), (p=0.752). Grade III-IV aGVHD was 5.3% (0.3–22.1%) in the $CD34^+$ selected subgroup and 7.3% (1.9–18%) in the unmodified subgroup at day 100 and 15.8% (3.7–35.6%) and 7.3% (1.9%−18%) at 1 year post-transplant (p=0.349).

Chronic graft-versus host disease

The incidence of cGVHD was significantly lower in the $CD34^+$ selected recipients. In the low risk group, the 1-year CI of cGVHD was 5.3% (0.9%−15.8%) in the $CD34^+$ selected subgroup and 47.8% (32.6–61.5%) in the unmodified subgroup, while the 3-year CI was 5.3% (0.9%−15.8%) and 56% (39.3%−69.8%), respectively (p<0.001).

In the high-risk group, none of the patients in the $CD34^+$ selected subgroup had cGVHD. The 1-year and 3-year CI of cGVHD in the unmodified subgroup were 24.4% (12.2–38.8%) and 27.6% (14.2–42.9%). Of note, none of the CD34 selected recipients in either risk group had extensive cGVHD.

Non-relapse mortality

There were no significant differences in NRM between the $CD34^+$ selected and unmodified groups. In the low risk group, the CI of NRM at day-100 was 10.3% (3.2–22.2%) in the $CD34^+$ selected subgroup and 10.9% (3.9–21.8%) in the unmodified subgroup. At 1-year the CI of NRM was 18.1% (7.8–31.7%) and 17.4% (8.1–29.7%), and at 3-years 32.4% (17.8–47.9%) and 28.2% (15.3–42.6%), respectively (p=0.939).

In the high-risk group, the CI of NRM at day-100 was 5.3% (0.3–22%) in the $CD34^+$ selected subgroup and 4.9% (0.9–14.7%) in the unmodified subgroup. At 1- year the CI was 26.3% (9.1–47.5%) and 14.6% (5.8–27.4%) and at 3-years 36.8% (15.7–58.3%) and 20% (9–34.1%), respectively (p=0.091).

The causes of death in the CD34$^+$ selected group were infections (41%), relapse (21%), graft failure (6%), GVHD (6%), toxicity (19%) and other causes (16%); and in the unmodified group: relapse (36%), GVHD (36%), infections (18%), graft failure (2.4%), toxicity (3.6%) and other causes (4%) (Table 5).

Relapse

In the low risk group, the relapse rate was similar between the CD34$^+$ selected and unmodified subgroups. The 1-year CI of relapse was 2.6% (0.2–12.1%) in the CD34$^+$ selected subgroup and 8.7% (2.7%−19.1%) in the unmodified subgroup, while the 3-year CI was 8.1% (2.0–19.9%) and 19.4% (8.8–33%), (p=0.187).

In the high-risk group, the relapse rate was lower in recipients of CD34$^+$ selected transplants. The 1-year CI of relapse was 21.1% (6.2–41.8%) in the CD34$^+$ selected subgroup and 58.5% (41.6–72.1%) in the unmodified subgroup, while the 3-year CI of relapse was 31.6% (12.2–53.2%) and 69.3% (51.6–81.6%), (p=0.007).

Overall survival, relapse-free survival and extensive chronic GVHD-Relapse-free survival (CRFS)

There were no significant differences in OS between both groups; however RFS was higher in the high-risk subgroup who had received CD34$^+$ selected transplants.

In the low risk group, the 1-year OS was 79.3% (62.8–89%) for the CD34$^+$ selected subgroup, and 78.3% (63.4–87.7%) in the unmodified subgroup, while the 3-year OS was 58.5% (40.5–72.8%) and 53.7% (36.9–67.9%) respectively (p=0.51) (Figure 1A). The 1-year RFS was 79.3% (62.8–89%) in the CD34$^+$ selected subgroup and 73.9% (58.7–84.3%) in the unmodified subgroup, while the 3-year RFS was 59.5% (41.7–73.4%) and 52.4% (35.8–66.5%),(p=0.448).

In the high-risk group, the 1-year OS was 57.9% (33.2–76.3%) for the CD34$^+$ selected subgroup and 34.1% (20.3–48.5%) in the unmodified subgroup, while the 3-year OS was 35.5% (15.2–56.6%) and 14.5% (5.5–27.7%) respectively (p=0.068) (Figure 1B). The 1-year RFS was 52.6% (28.7–71.9%) in the CD34$^+$ selected subgroup and 26.8% (14.5–40.8%) in the unmodified subgroup, while the 3-year RFS was 31.6% (12.9–52.2%) and 10.7% (3.5–22.7%), (p= 0.045).

Due to the differences in RFS between CD34$^+$ selected and unmodified patients in the high risk group, Cox proportional hazard regression models were fit to evaluate potential differences in RFS due to cytogenetic risk at diagnosis (poor vs. very poor), blasts at transplant (<5% vs. 5–9%), donor type (match vs. mismatch), conditioning intensity (MAC vs. RIC) and type of transplant (CD34 selected vs. unmodified) (table 4). In univariate analysis, patients with very poor cytogenetic risk at diagnosis (HR = 2.18, 95% CI 1.21–3.92, p=0.009) and patients receiving unmodified transplants (HR = 1.84, 95% CI 1.00–3.37, p=0.049) were at significantly greater risk of relapse or death. However, in a multivariate model adjusting for both cytogenetic risk and transplant type, cytogenetic risk remained the

only significant covariate predicting for worse RFS (HR = 1.95, 95% CI 1.07–3.58, p=0.030) while type of transplant was non significant (p=0.176).

The CRFS was significantly higher in the recipients of $CD34^+$ selected transplant. In the low risk group, the 1-year CRFS was 79.3 % (62.8–89%) for the CD34 selected subgroup and 32.6% (19.7–46.1%) in the unmodified subgroup, while the 3-years CRFS was 59.5% (41.7–73.4%) and 19.2% (8.8–32.6%) respectively (p<0.001) (Figure 2A). In the high-risk group, the 1-year CRFS was 52.6% (28.7–71.9%) for the $CD34^+$ selected subgroup and 12.2% (4.5–24.1%) in the unmodified subgroup, while the 3-year CRFS was 31.6% (12.9–52.2%) and 6.1% (1.2–17%), (p=0.001) (Figure 2B). Cox proportional hazard regression models were fit to evaluate potential differences in CRFS in a similar fashion described above for RFS (table 4). In univariate and multivariate models, both cytogenetic risk (MV HR = 1.82, 95% CI 1.01–3.29, p=0.048) and transplant type (MV HR = 2.31, 95% CI 1.22–4.40, p=0.010), were significant covariate predicting for worse CRFS.

Discussion

This retrospective study comparing $CD34^+$ selected and unmodified transplants, demonstrates that in patients with advanced MDS, the OS was similar between the two transplant methods, though with a significantly lower incidences of chronic GVHD and without an increased relapse rate, and as a result, a better composite outcome of CRFS after $CD34^+$ selected transplants. We attempted to compare two similar cohorts and to include in the analysis all the factors that may contribute to differences in outcomes. However, we recognize the limitation of a retrospective analysis and the use of cohorts from two different institutions. We specifically acknowledge that conditioning intensity and the use of ATG in the unmodified cohort may be factors that can affect outcomes, though in this analysis they were found not to be significant.

This study confirms previous observations that the incidence of acute and chronic GVHD are lower in recipients of $CD34^+$ selected transplants[20,21], despite a higher proportion (24%) of mismatch donors in this cohort. An unexpectedly low CI of aGVHD was seen in the high-risk subgroup of recipients of unmodified transplants; similar to that of $CD34^+$ selected recipients, but lower than the CI in recipients of unmodified transplants in the low risk subgroup. This lower incidence of aGVHD in this unmodified subgroup was seen despite similar proportion of related and unrelated donors, use of ATG and use of MAC regimens. A likely explanation is that the lower incidence of GVHD seen in this group was secondary to a higher relapse rates since relapse and GVHD were competing risks. Although the incidence of grade II-IV acute GvHD was lower in the CD34-selected group, the incidence of grade III - IV was similar between the two cohorts, suggesting that when acute GVHD occurs after a $CD34^+$ selected graft it tends to present in a more aggressive way.

Chronic GVHD was markedly low after CD34 selected transplant in both the low risk and high risk-groups despite using peripheral blood stem cells in nearly all patients. The largest phase 3 randomized multicenter trial comparing PB to BM graft showed a high incidence of extensive chronic GVHD of 53% in patients who received unmodified PB grafts[30] and of 41% in those who received BM graft. Both are still about one log higher than the cGVHD

seen after CD34+ selected graft (5%), despite using a PBSC graft source in almost all patients.

NRM was similar in recipients of CD34+ selected and unmodified graft regardless of the disease risk subgroup; however the distribution of causes of death was different. Infections were the most common primary cause of NRM in the CD34+ selected group, while GVHD was the most common primary cause of NRM in the unmodified group. Infections were also a major complication after unmodified transplant as they were the most common secondary cause of death in recipients of unmodified graft developing GVHD. The basis for this difference after CD34+ selection is the delayed immune reconstitution since this method eliminates all subsets of mature T cells. The process of generation of a new functional immune system de- novo takes several months and, at times, up to 1 to 2 years post transplant [31,32,33]. Therefore, infections and particularly viral reactivation, such as CMV, EBV, adenovirus and others remain a major challenge after CD34+ transplants. Adoptive immunotherapy with donor derived or third-party viral specific cytotoxic T cells has been used both after unmodified and CD34+ selected allo-HSCT with varying level of success[34, 35, 36,37,38,39,40], however, the low incidence of GVHD and lack of immune suppressive medications post CD34+ selected allo-HSCT make it an ideal setting for this type of therapy.

Early studies comparing ex vivo T cell depleted with unmodified transplants reported significantly higher relapse rates in CD34+ selected transplant[41]. However, the intensity of the preparative regimen in some of these studies was non-myeloablative and the T cell depletion techniques were different from CD34+ selection. More recently, the only devices licensed for T cell depletion are based on CD34+ selection. A recent prospective study7 and several retrospective analysis using myeloablative conditioning regimen and CD34+ cell selection with the Miltenyi CliniMACS device and without pharmacological GVHD prophylaxis[15,13] reported relapse rates of 20.6% at 1 year for AML in CR1, 11.8% for MDS, and 23% for ALL, which are similar to relapse rates reported for unmodified transplants [42, 43,44.] In this comparative analysis, there was no difference in relapse rate among the low risk patients but there was a higher incidence of relapse among the poor risk patients receiving unmodified transplants. Further, in a multivariate RFS model including cytogenetic abnormalities at diagnosis and transplant type for the high risk cohort, only cytogenetics remained significantly associated with the outcome. This is in agreement with other reports emphasizing the importance of cytogenetic abnormalities on transplant outcome [15, 45,46,47]. Post-transplant Interventions to reduce the incidence of relapse are being explored both after unmodified and CD34+ selected transplants[48, 49], this type of intervention has the potential to also affect GVHD incidence by affecting different subsets of T cells.

Overall survival was similar for recipients of CD34+ selected and unmodified grafts as reported in similar comparison studies in patients with AML and ALL[20,21].However, the composite end point of survival without relapse and without chronic GVHD was significantly higher for recipients of CD34+ selected transplants. In recent years it became evident that the routinely used parameters to assess transplant outcomes, i.e. survival, relapse, GVHD and NRM lack the ability to assess cure without ongoing morbidity. Composite end points acknowledge that both survival and rates of other critical events are

important when testing new therapies[50] and this composite endpoint has been incorporated into outcomes reports also in the field of BMT more recently[51, 52]. We believe that the ongoing multicenter study sponsored by the BMT CTN (BMT CTN 1301, NCT 02345850) will have the ability to address the issues raised in this analysis in a prospective manner. This study is comparing unmodified allo-HSCT with GVHD prophylaxis using tacrolimus and methotrexate vs. $CD34^+$ selected allo-HSCT vs. allo-HSCT with post-transplant cyclophosphamide, using only myeloablative conditioning regimen, with the primary end point being CRFS.

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Highlights

- A retrospective analysis comparing unmodified to CD34+ selected allo-HCT in MDS.
- The composite end-point of survival without relapse and without chronic GVHD was higher in the CD34+ selected group.
- Relapse is affected by high risk cytogenetic and not by type of transplant.

1A 1B

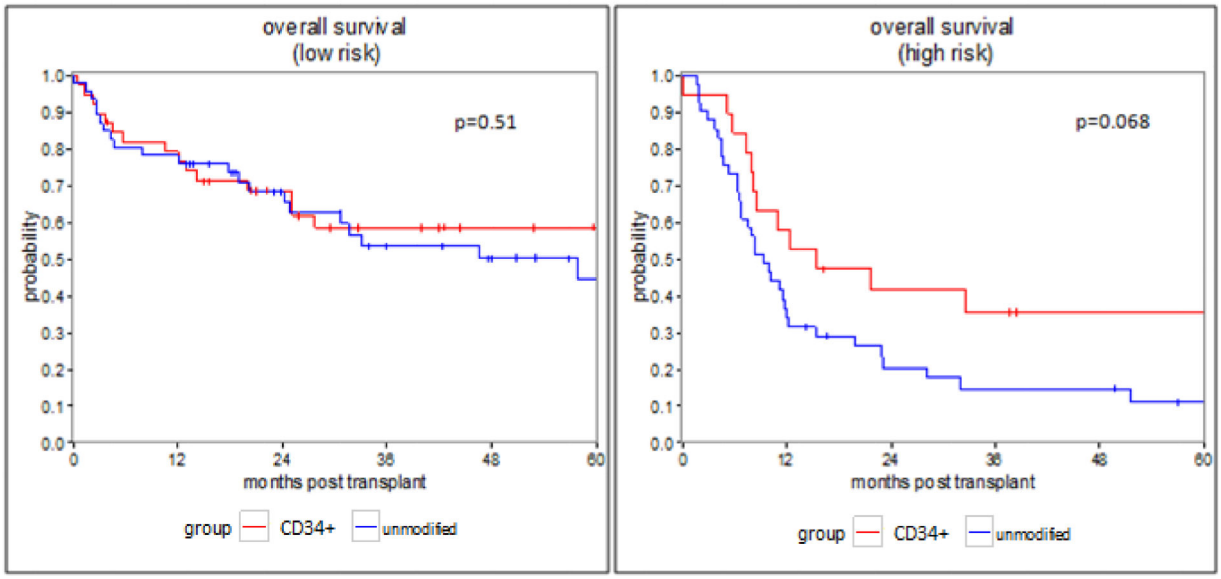

Figure 1: Overall Survival

Figure 1: overall survival in patients who underwent CD34+ selected and unmodified allo-HSCT.

1A: OS in the low risk group, 1B: OS in the high risk group

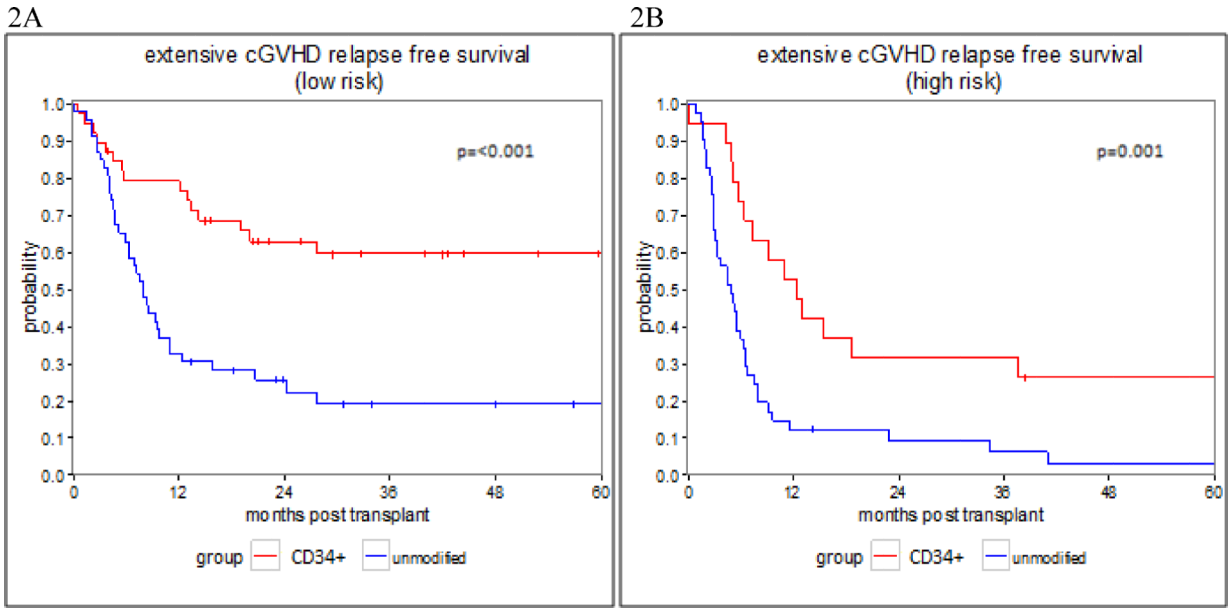

Figure 2: CRFS- extensive chronic GVHD and relapse free survival

Figure 2: Extensive chronic GVHD and relapse free survival in patients who underwent CD34+ selected and unmodified allo-HSCT.

2A: CRFS in the low risk group, 2B: CRFS in the high risk group

Table 1:

*Patients and transplant characteristics

Characteristics	CD34+ SELECTED (N=60), MSKCC cohort	Unmodified (N=121) MDACC cohort	p-value
Median follow-up, months (range)	43.4 (3.8–119.5)	50.2 (12.2–136.3)	
Age, years (range)	57.1 (21.9–72)	57 (19–72)	0.585
Female gender	34 (56.7%)	40 (33.1%)	0.004
MDS-t	7 (11.7%)	38 (31.4%)	0.007
Cytogenetic risk at diagnosis (IPSS-R)			0.016
Good	25 (42.4%)	47 (38.8%)	
Intermediate	15 (25.4%)	18 (14.9%)	
Poor	11 (18.6%)	14 (11.6%)	
Very poor	8 (13.6%)	42 (34.7%)	
Missing	1		
Blasts at transplant			< 0.001
< 5%	48 (81.4%)	53 (46.1%)	
5–9%	11 (18.6%)	34 (29.6%)	
10–19%	0	28 (24.3%)	
Missing	1	6	
Donor type			< 0.001
MRD	21 (35.0%)	62 (51.2%)	
MUD	25 (41.7%)	59 (48.8%)	
MMD	14 (23.3%)	0	
Stem cell source			0.001
BM	5 (8.3%)	39 (32.2%)	
PB	55 (91.7%)	82 (67.8%)	
Conditioning regimen			<0.001
MAC	60 (100%)	81 (66.9%)	
RIC	0	40 (33.1%)	
ATG in conditioning regimen	60 (100%)	59 (48.8%)	
Time from diagnosis to transplant (months)	8.2 (1.8–161.1)	7.4 (0.9–53)	0.314

*The initial cohort included 181 patients. Due to large differences between the MSKCC (CD34+ selected group) and MDACC (unmodified group) the analysis was limited to 145 patients (table 2). MDS-t= therapy related MDS, MRD=matched related donor, MUD= matched unrelated donor, MMD= mismatched donor, BM= bone marrow, PB= peripheral blood, MAC= myeloablative, RIC= reduced intensity

Table 2:

Patients and transplant characteristics in the 'low' and 'high' risk subgroups

	Good or intermediated cytogenetic risk at diagnosis&<10% blasts			Poor or very poor cytogenetic risk at diagnosis&<10% blasts		
	CD34 SELECTED (N=39) MSKCC cohort	Unmodified (N=46) MDACC cohort	P value	CD34 SELECTED (N=19) MSKCC cohort	Unmodified (N=41) MDACC cohort	P value
Median follow-up, month (range)	43.4 (3.8–109.2)	44.9 (12.9–115.6)	-	52.0 (16.2–119.5)	53.3 (14.2–93.9)	-
Age, years (range)	56.9 (21.9–72)	55.5 (25–69)	0.357	59.2 (26.7–69)	58 (32–72)	0.994
Female gender	23 (59.0)	17 (37.0)	0.071	9 (47.4)	13 (31.7)	0.377
MDS-t	3 (7.7)	8 (17.4)	0.316	4 (21.1)	16 (39.0)	0.280
Cytogenetic risk at diagnosis			0.148			0.042
Good	24 (61.5)	36 (78.3)		-	-	
Intermediate	15 (38.5)	10 (21.7)		-	-	
Poor	-	-		11 (57.9)	11 (26.8)	
Very poor	-	-		8 (42.1)	30 (73.2)	
Blasts at transplant			0.465			0.016
< 5%	30 (76.9)	31 (67.4)		17 (89.5)	22 (53.7)	
5–9%	9 (23.1)	15 (32.6)		2 (10.5)	19 (46.3)	
Donor type			0.001			0.008
Match related	15 (38.5)	25 (54.3)		5 (26.3)	21 (51.2)	
Match unrelated	14 (35.9)	21 (45.7)		10 (52.6)	20 (48.8)	
Mismatch	10 (25.6)	0		4 (21.1)	0	
Graft type			0.010			0.012
Bone marrow	4 (10.3)	16 (34.8)		1 (5.3)	15 (36.6)	
Peripheral blood	35 (89.7)	30 (65.2)		18 (94.7)	26 (63.4)	
Conditioning intensity			< 0.001			0.010
Myeloablative	39 (100.0)	31 (67.4)		19 (100.0)	27 (65.9)	
Reduced intensity	0	15 (32.6)		0	14 (34.1)	
ATG in conditioning regimen	39 (100.0)	21 (45.7)		19 (100.0)	20 (48.8)	
Time from diagnosis to transplant, month	12.1 (2.5–161.1)	9.5 (2.3–53)	0.884	7.9 (1.8–28.8)	5.9 (1.5–42.9)	0.499

MDS-t= therapy related MDS, MRD=matched related donor, MUD= matched unrelated donor, MMD= mismatched donor, BM= bone marrow, PB= peripheral blood, MAC= myeloablative, RIC= reduced intensity

Table 3:

Transplant outcomes in ‘low’ and ‘high’ risk subgroups

	Good or intermediated cytogenetic risk at diagnosis & <10% blasts			Poor or very poor cytogenetic risk at diagnosis & <10% blasts		
	CD34 SELECTED (N=39) MSKCC cohort	Unmodified (N=46) MDACC cohort	P value	CD34 SELECTED(N=19) MSKCC cohort	Unmodified (N=41) MDACC cohort	P value
AGVHD (grade II–IV)			0.015			0.752
day 100	12.8% (4.6–25.4)	41.3% (26.9–55.1)		15.8 %(3.7–35.6)	22% (10.7–35.7)	
1 year	18.0% (7.8–31.7)	41.3% (26.9–55.1)		31.6% (12.3–53)	24.4%(12.5–38.4)	
AGVHD (grade III–IV)						0.349
day 100	12.8% (4.6–25.4)	13.0% (5.2–24.5)		5.3%(0.3–22.1)	7.3% (1.9–18)	
1 year	15.4% (6.1–28.5)	15.2% (6.6–27.1)		15.8%(3.7–35.6)	7.3% (1.9–18)	
CGVHD			< 0.001			0.013
1 year	5.3% (0.9–15.8)	47.8% (32.6–61.5)		0%	24.4%(12.2–38.8)	
3 year	5.3% (0.9–15.8)	56% (39.3–69.8)		0%	27.6%(14.2–42.9)	
NRM			0.939			0.091
100 day	10.3% (3.2–22.2)	10.9 %(3.9–21.8)		5.3%(0.3–22)	4.9%(0.9–14.7)	
1 year	18.1%(7.8–31.7)	17.4% (8.1–29.7)		26.3%(9.1–47.5)	14.6%(5.8–27.4)	
3 year	32.4%(17.8–47.9)	28.2% (15.3–42.6)		36.8%(15.7–58.3)	20%(9–34.1)	
Relapse			0.187			0.007
1 year	2.6% (0.2–12.1)	8.7% (2.7–19.1)		21.1%(6.2–41.8)	58.5%(41.6–72.1)	
3 year	8.1%(2.0–19.9)	19.4% (8.8–33.0)		31.6%(12.2–53.2)	69.3%(51.6–81.6)	
RFS			0.448			0.045
1 year	79.3% (62.8–89)	73.9% (58.7–84.3)		52.6%(28.7–71.9)	26.8%(14.5–40.8)	
3 year	59.5 %(41.7–73.4)	52.4% (35.8–66.5)		31.6%(12.9–52.2)	10.7%(3.5–22.7)	
OS			0.51			0.068
1 year	79.3 %(62.8–89)	78.3%(63.4–87.7)		57.9% (33.2–76.3)	34.1%(20.3–48.5)	
3 year	58.5% (40.5–72.8)	53.7%(36.9–67.9)		35.5%(15.2–56.6)	14.5%(5.5–27.7)	
CRFS			<0.001			0.001
1 year	79.3% (62.8–89)	32.6%(19.7–46.1)		52.6% (28.7–71.9)	12.2% (4.5–24.1)	
3 year	59.5% (41.7–73.4)	19.2% (8.8–32.6)		31.6% (12.9–52.2)	6.1% (1.2–17.0)	

Table 4:

Factors Relating to RFS and CRFS in the ‘high risk’ subgroup

	univariate		multivariate	
RFS				
	HR (95% CI)	p-value	HR (95% CI)	p-value
cytogenetic risk at diagnosis		0.009		0.030
Poor	reference		reference	
very poor	2.18 (1.21, 3.92)		1.95 (1.07, 3.58)	
blasts at transplant		0.877		
< 5 %	reference			
5–9 %	1.05 (0.59,1.85)			
donor type		0.250		
Match	reference			
Mismatch	0.50 (0.16,1.62)			
conditioning intensity		0.102		
Myeloablative	reference			
RIC	1.72 (0.90, 3.30)			
transplant type		0.049		0.176
CD34 SELECTED	reference		reference	
Unmodified	1.84 (1.00, 3.37)		1.54 (0.82, 2.88)	
CRFS				
	HR (95% CI)	p-value	HR (95% CI)	p-value
cytogenetic risk at diagnosis		0.007		0.048
Poor	reference		reference	
very poor	2.21 (1.24, 3.93)		1.82 (1.01, 3.29)	
blasts at transplant		0.455		
< 5 %	reference			
5–9 %	1.24 (0.71, 2.15)			
donor type		0.138		
Match	reference			
Mismatch	0.41 (0.13, 1.33)			
conditioning intensity		0.147		
Myeloablative	reference			
RIC	1.61 (0.85, 3.08)			
transplant type		0.002		0.010
CD34 SELECTED	reference		reference	
Unmodified	2.68 (1.43, 5.01)		2.31 (1.22, 4.40)	

	univariate	multivariate
Graft source	0.363	
BM	reference	
PBSC	0.76 (0.42, 1.38)	

Table 5:

Causes of death in the two cohorts

Cause Of Death	CD34+ Selected (N=31) MSKCC cohort	Unmodified (N=57) MDACC cohort
Relapse	8 (25%)	36 (63%)
Infection	10 (32%)	8 (14%)
Bacterial	5	2
Viral	2	4
Fungal	2	
PCP	1	
Unspecified		2
GVHD	4 (13%)	8 (14%)
Graft failure	1 (3.0%)	1 (2%)
Toxicity	3 (10%)	3 (5%)
Other	5 (17%)	1 (2%)