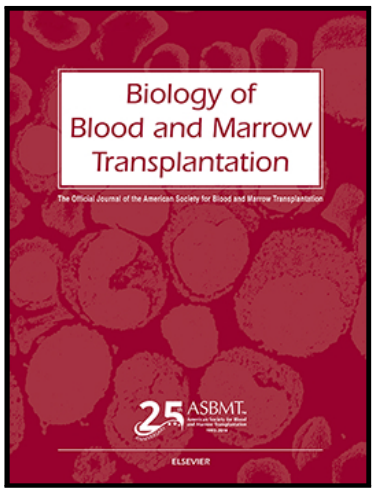

Comparable Long-Term Outcome after Allogeneic Stem-Cell Transplantation from Sibling and Matched Unrelated Donors in AML Patients Older than 50 years. A Report on Behalf of the ALWP of EBMT

Avichai Shimoni , Myriam Labopin , Bipin Savani , Michael Byrne , Liisa Volin , Jürgen Finke , Dietger Niederwieser , Gerhard Ehninger , Didier Blaise , Dietrich Beelen , Reza Tabrizi , Henrik Sengeloev , Arnold Ganser , Jan J. Cornelissen , Mohamad Mohty , Arnon Nagler

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Highlights

- Marked improvement has been achieved in recent years in SCT from unrelated donors
- Long-term outcome is equivalent after SCT from unrelated and sibling donors
- Patients who are leukemia-free 2 years after SCT can expect a favorable outcome

Comparable Long-Term Outcome after Allogeneic Stem-Cell Transplantation from Sibling and Matched Unrelated Donors in AML Patients Older than 50 years. A Report on Behalf of the ALWP of EBMT.

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Running Title: Long term outcome after SCT

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Abstract

Allogeneic stem-cell transplantation (SCT) is potentially curative therapy in acute myeloid leukemia (AML). Marked improvement has been achieved with SCT from matched unrelated-donors (MUD) in recent years. However, there is limited data comparing the long-term outcomes (beyond 10 years) after SCT from sibling donors and MUDs in older AML patients. We analyzed these outcomes in a large cohort of AML patients (n=1134), age ≥50 years, who were alive and leukemia-free 2 years after SCT from matched siblings (n=848) or MUD (n=286), with a median follow up 8.9 years. The median age was 56 and 58 years, after SCT from sibling and MUDs, respectively (P=0.005). 77%, 12% and 11% in the sibling group were in CR1, CR2 and active leukemia at SCT compared to 50%, 25% and 25% in the MUD group, respectively (P<0.001). 61% of sibling, and 62% of MUDs had reduced-intensity conditioning (P=0.78). The 10-year leukemia-free survival (LFS) of patients surviving leukemia-free 2 years after SCT was 72% and 62%, respectively (P=0.30). Multivariate-analysis identified active leukemia at SCT (HR 1.86, P=0.0001) or CR2 (HR 1.51, P=0.02) compared to CR1, female recipient (HR 0.71, P=0.006), adverse cytogenetics (HR 2.52, P=0.01) and prior GVHD (HR 1.31, P=0.04) as independent factors predicting LFS. Donor and conditioning type were not significant. The cumulative incidence of late relapse was 15% and 17% (P=0.97) and of late non-relapse mortality, 13% and 21%, respectively (P=0.15). Long-term LFS is similar and patients who are leukemia-free 2 years after SCT can expect favorable outcomes with both donor types.

Key words: Acute myeloid leukemia, allogeneic stem cell transplantation, long-term outcome, sibling, unrelated donor.

Introduction

Allogeneic hematopoietic stem-cell transplantation (SCT) is a potentially curative approach in patients with acute myeloid leukemia (AML). A growing proportion of SCT recipients are becoming long-term survivors due to advances in supportive care and transplantation techniques over the last several years.[1] These improvements are most apparent in the SCT outcomes from matched unrelated donors (MUD).[2-4] Improved patient selection, transplantation earlier in the disease course, high-resolution HLA typing, an enhanced understanding of acute graft-versus-host disease (GVHD) risk factors, and larger, more diverse donor registries have all led to better patient outcomes.[5,6] Furthermore, the development and refinement of reduced-intensity conditioning (RIC) regimens significantly reduced GVHD and post-SCT infectious complications making SCT safer and more attractive for older patients due to reduced non-relapse mortality (NRM). These improved outcomes, and the increased likelihood of identifying a suitable matched donor, resulted in an increase in the number of unrelated donor transplants and MUD is now the most commonly used graft source.[7] In total, these advances led to an increase in the median age of MUD transplant recipients.

Most deaths after SCT occur within the first 2 years.[8] Long-term survivors are at increased risk for late complications as well as late morbidity and mortality that is higher than their sibling donors or the age- and gender-matched general population.[9-11] In the largest study of long-term survivors, the Center of International Blood and Marrow Transplantation Research (CIBMTR) showed that 85% of SCT patients, and 84% of AML patients, who were alive and disease-free at 2 years after SCT would remain alive 10 years.[10] Relapse was the most common cause of late death, but chronic GVHD, infections, organ toxicity and second cancers were also important contributors of late mortality. These observations were limited to recipients of myeloablative conditioning (MAC). There is a paucity of data on the kinetics of late events and long-term survival after RIC. In addition, transplants were performed in the years 1980-2003, the median age of transplant recipients was 28 years, and only 18.5% of transplants were from MUDs. More recently, older patients make up the majority of SCT recipients and MUDs are the most prevalent donor source.

In a previous study from the acute leukemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT), we showed that the long-term survival was similar in older patients (>50 years) after RIC and MAC

SCT from HLA-matched siblings. While relapse was the major cause of late deaths irrespective of conditioning intensity, NRM, particularly due to chronic GVHD and second malignancies, was more prevalent after MAC.[12]

In the current study we extended the analysis to MUDs and compared late events and long-term outcomes of patients that underwent SCT from a matched sibling donor and MUD in a more contemporary era. We show that 2-year survivors after MUD SCT experience similarly favorable outcomes as matched sibling donor recipients.

Patients and Methods

Study design and data collection

This is a retrospective multicenter analysis. Data were provided and approved for this study by the ALWP of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centers mainly in Europe that are required to report all consecutive SCTs and their follow-up once a year. Data are entered, managed and maintained in a central database with internet access; each EBMT center is represented in this database. Audits are routinely performed to determine the accuracy of the data. All patients or legal guardians are provided informed consent according to the Declaration of Helsinki. The Review Board of the ALWP of the EBMT approved this study. Eligibility criteria for this study included age ≥50 years, de-novo AML in any disease status at SCT, transplants from HLA-compatible sibling donor or a matched unrelated donor (MUD) between the years 2000 and 2007 with bone-marrow (BM) or granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem-cells (PBSC) after MAC or RIC. Patients given mismatched-unrelated, haplo-identical or umbilical cord blood grafts were not included. Variables collected included recipient and donor characteristics, disease features, transplant related factors including drugs and total doses used in the conditioning regimen, and outcome variables.

Conditioning regimens

The conditioning regimen was selected according to the participating center discretion. Dose intensity was defined according to EBMT criteria based on the reversibility and expected duration of cytopenia after SCT.[13] MAC consisted of high-dose cyclophosphamide and high-dose busulfan (BuCy) or total body irradiation (TBI). Reduced-toxicity myeloablative regimens consisted of a combination of

fludarabine and myeloablative dose of an alkylating agent (such as intravenous busulfan at a total dose ≥9.6 mg/kg, melphalan >140 mg/m2, treosulfan ≥ 36 gr/m2) and were included with MAC. RIC consisted of fludarabine combined with reduced dose alkylating agent (Such as busulfan < 9.6 mg/kg) or low-dose TBI (<8 Gy). GVHD prophylaxis consisted of cyclosporine A and a short course of methotrexate in most patients. In-vivo T-cell depletion) with anti-thymocyte globulin (ATG) or alemtuzumab was allowed according to the participating center policy.

Statistical analysis

Landmark analysis was performed in order to evaluate the impact of prognostic variables on the outcome of patients who were alive and without evidence of relapse at 2 years after SCT.[14] The primary study endpoint was leukemia-free survival (LFS). Secondary endpoints were relapse incidence, NRM, overall Survival (OS) and GVHD-free relapse free survival (GRFS). Disease relapse was defined according to standard hematological criteria. NRM was defined as death of any cause in the absence of prior disease recurrence. LFS was defined as survival without relapse. Overall survival was calculated from the day of SCT until death of any cause or last follow-up. GRFS was defines as survival with no relapse, death or extensive chronic GVHD after 2 years from SCT. Patients with no event were censored at last contact. The cause of death was categorized according to standard criteria. Patient, disease, and transplant-related characteristics for the two cohorts (matched sibling/MUD) were compared by using χ^2 statistics for categorical variables and the Mann-Whitney test for continuous variables. Cumulative incidence functions (CIF) were used to estimate relapse incidence and NRM in a competing risks setting, with death and relapse considered as competing events with each other.[15] The probabilities of LFS and OS were calculated using the Kaplan-Meier method. For incidence of specific cause of death, death due to another cause was the competing event. Univariate analyses were done using the Gray's test for cumulative incidence functions and the log rank test for OS and LFS. A Cox proportional hazards model was used for multivariate regression. All variables differing significantly between the 2 groups or factors associated with one outcome in univariate analysis were included in the Cox model. To test for a center effect, we introduced a random effect or frailty for each center into the model. For all univariate analyses, continuous variables were categorized and the median used as a cut-off point. Results were expressed as the hazard ratio (HR) with the 95%

confidence interval (95% CI). All interactions between donor type and other variables were studied. All P values were two-sided and values < 0.05 were considered statistically significant. Statistical analyses were performed with SPSS 24.0 (Inc., Chicago) and R 3.4.1 software packages (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Results

Patient characteristics

Patient, disease and SCT characteristics are outline in Table 1. A total of 1134 patients were included in the analysis; 848 patients had matched sibling donors and 286 had a MUD. Some patients were reported in a previous analysis.[12] All patients were alive and leukemia-free at the landmark point, 2 years after SCT. The median age at SCT was 56 years (50–75) and 58 years (range, 50-74) after matched sibling and MUD SCT, respectively (P=0.005). Eleven percent of sibling SCT recipients had advanced disease at transplant compared with 25% of MUD recipients. The percentage of patients in CR1 and CR2 was 89% and 75%, respectively (P=0.0001). The use of RIC was similar in both donor groups. In all, 44% of all patients had some form of T-cell depletion. The majority had in-vivo T-cell depletion with either ATG (25%) or alemtuzumab (13%) and a small subset had ex-vivo T-cell depletion (6%). T-cell depletion was used more often in the MUD group (71% Vs 34%, respectively, P<0.0001). Sibling donor recipients were more likely to receive PBSC rather than BM (88% Vs. 83%, P=0.04). In all, 59% of patients had chronic GVHD prior to the 2-year landmark that was limited in 25% and extensive in 34%. The median year of transplant for patients in the sibling group was 2005 (range, 2000-2007) while patients in the MUD group were transplanted more recently, median year 2006 (range, 2000-2007, P<0.0001). The median follow-up was 9.04 years (range, 2-16.4), and 8.5 years (range, 2.4-15.6), respectively. The univariate outcomes after SCT are presented in Table 2.

Table 1: Patient Characteristics

	Sibling (n=848)	Matched unrelated (n=286)	P-value
Age (median, years)	56 (50-75)	58 (50-74)	0.005
Gender (male)	434 (51%)	155 (54%)	0.38
F → M	180 (21%)	36 (13%)	0.002
Cytogenetics Good Intermediate Poor Missing	 50 (6%) 471 (55%) 72 (8%) 255 (30%)	 17 (6%) 134 (47%) 33 (12%) 102 (36%)	0.06
Status at SCT CR1 CR2 Advanced	 652 (77%) 104 (12%) 92 (11%)	 142 (50%) 72 (25%) 72 (25%)	< 0.0001
Stem cell source (PBSC)	744 (88%)	237 (83%)	0.04
Conditioning MAC RIC	 328 (39%) 520(61%)	 108 (38%) 178 (62%)	0.78
T-cell depletion	266 (34%)	190 (71%)	< 0.0001
Patient CMV +	509 (68%)	178 (70%)	0.46
Donor CMV +	463 (62%)	110 (43%)	< 0.0001
Year of SCT (median, range)	2005 (2000-2007)	2006 (2000-2007)	< 0.0001
Prior aGVHD (grade II-IV)	174 (21%)	55 (20%)	0.64
Prior cGVHD Limited Extensive Unknown grade	470 (61%) 180 284 6	142 (53%) 75 65 2	0.02

Abbreviations: F → M, female donor to male recipient; SCT, stem cell transplantation; PBSC, peripheral blood stem cell; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; GVHD, graft-versus-host disease; aGVHD, acute GVHD; cGVHD, chronic GVHD.

Table 2: Univariate analysis of late transplantation outcomes in patients surviving leukemia-free two years after transplantation.

	Relapse		NRM		LFS	
	Rate	P	Rate	P	Rate	P
Donor Sibling	15 (13-18)	0.97	13 (11-16)	0.15	72 (68-75)	
MUD	17 (12-22)		21 (15-28)		62 (55-70)	
Age ≤56 years	14 (11-17)	0.57	11 (8-14)	0.003	75 (71-79)	0.009
>56 years	17 (14-21)		20 (16-24)		63 (58-68)	
Gender male	17 (14-21)	0.0003	18 (14-22)	0.007	65 (60-70)	0.0003
female	14 (11-17)		12 (9-15)		75 (70-79)	
F → M yes	17 (12-23)	0.48	19 (13-26)	0.14	64 (57-72)	0.10
no	15 (13-18)		14 (11-17)		71 (68-74)	
Cytogenetics						
Good	6 (1-14)	0.05	17 (8-28)	0.28	78 (67-89)	0.09
Intermediate	16 (13-20)		12 (10-16)		71 (67-75)	
Poor	21 (13-30)		16 (9-25)		63 (52-73)	
Missing	14 (10-18)		19 (14-24)		68 (62-74)	
Status at SCT						
CR1	13 (11-16)	0.0003	13 (10-16)	0.02	74 (71-78)	<0.0001
CR2	18 (12-25)		18 (12-26)		64 955-73)	
Advanced	25 (18-32)		20 (14-28)		55 (46-64)	
Stem cell source						
PBSC	16 (14-19)	0.57	15 (13-18)	0.35	69 (65-72)	0.27
BM	13 (8-19)		13 (8-19)		74 (67-82)	
Conditioning						
RIC	16 (13-19)	0.52	15 (12-19)	0.62	69 (65-73)	0.39
MAC	15 (11-19)		14 (11-18)		71 (66-76)	
T-cell depletion						
yes	17 (13-21)	0.58	13 (10-17)	0.17	70 (65-75)	0.62
no	15 (12-18)		16 (13-20)		69 (65-74)	
Patient CMV						
Positive	15 (12-18)	0.21	15 (12-18)	0.58	70 (66-74)	0.56
Negative	18 (13-22)		14 (10-20)		68 (62-74)	
Donor CMV						
Positive	14 (11-18)	0.14	14 (11-18)	0.99	71 (67-76)	0.24
Negative	18 (14-22)		15 (11-19)		68 (63-73)	
Year of SCT						
≤2005	17 (14-21)	0.05	13 (10-16)	0.04	70 (66-74)	0.86
>2005	12 (9-16)		22 (12-34)		66 (55-76)	

Prior aGVHD						
yes	14 (10-20)	0.26	17 (11-23)	0.31	69 (62-76)	0.86
no	16 (13-19)		14 (12-17)		70 (66-73)	
Prior cGVHD						
yes (all grades)	15 (12-18)	0.23	19 (15-23)	<0.0001	66 (62-70)	0.01
limited	17 (13-23)		13 (8-19)		69 (63-76)	
extensive	14 (10-18)		23 (18-28)		63 (57-69)	
no	17 (14-21)		8 (5-11)		75 (70-79)	

Abbreviations: as in Table 1. NRM, non-relapse mortality; LFS, leukemia-free survival; MUD, matched unrelated donor; BM, bone marrow.

LFS, OS and GRFS

The 10-year LFS of patients alive and leukemia-free 2-years after SCT was 72% (95%CI, 68-75) and 62% (95%CI, 55-70) after matched sibling and MUD transplants, respectively (Fig. 1A, P=0.30). Inferior LFS was observed in older patients, male patients, individuals with advanced leukemia at SCT and patients with prior chronic GVHD (Table 2). Table 3 outlines the multivariable analysis of factors predicting long-term outcomes. Multivariate-analysis identified active leukemia at SCT (HR 1.86, P=0.0001) or CR2 (HR 1.51, P=0.02) compared to CR1, female recipient (HR 0.70, P=0.006), adverse cytogenetics (HR 2.51, p=0.01) and prior chronic GVHD (HR 1.31, p=0.04) as independent factors predictive of inferior LFS. The donor type, conditioning regimen and age, were not significant. Both limited and extensive prior chronic GVHD were associated with lower LFS, as both were associated increased NRM and with no protection from late relapse. However, the negative effect of chronic GVHD was more pronounced in those having extensive grade.

The 10-year OS was 74% (95%CI, 70-77) and 66% (95%CI, 60-74) after sibling and MUD transplants, respectively (Fig. 1B, P=0.42). Similarly, the multivariate-analysis identified active leukemia at SCT (HR 1.85, P=0.0003) or CR2 (HR 1.41, P=0.08) compared to CR1, female recipient (HR 0.68, P=0.004), adverse cytogenetics (HR 2.63, p=0.01) and prior chronic GVHD (HR 1.42, p=0.01) as independent predictors of inferior OS (data not shown).

The 10-year GRFS was 63% (95% CI: 59 - 66). It was 65% (95%CI, 61-68) and 57% (95%CI, 50-65) after sibling and MUD transplants, respectively (P=0.47). Similarly to the analysis of OS, the multivariate-analysis identified active leukemia at SCT (HR 1.66, P=0.009) or CR2 (HR 1.39, P=0.05) compared to CR1, female recipient (HR 0.73, P=0.009), adverse cytogenetics (HR 2.04, p=0.01) and chronic

GVHD prior to the 2-year landmark (HR 1.33, p=0.02) as independent predictors of inferior OS (data not shown).

Figure 1A

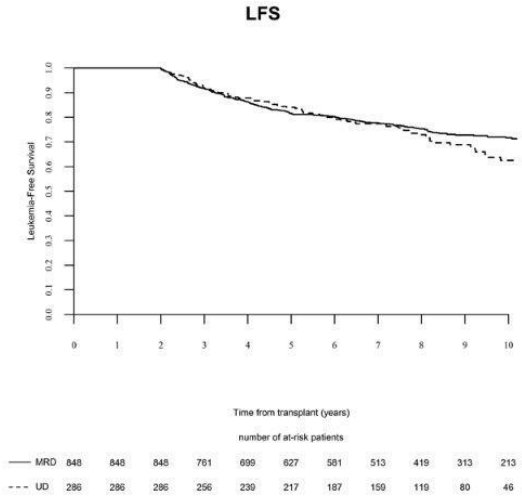

Figure 1B

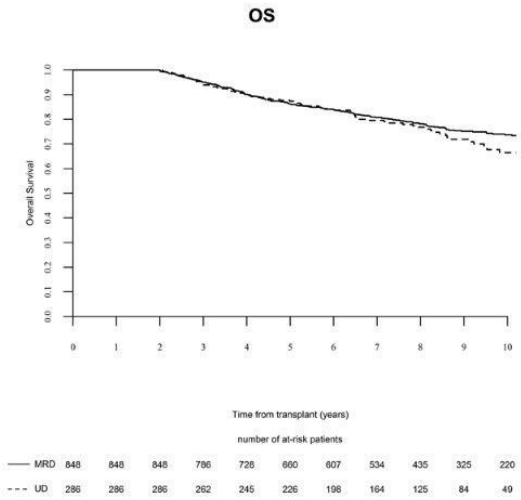

Figure 1. Subsequent outcomes of patients who were leukemia-free 2 years after stem cell transplantation by donor source. Leukemia-free survival (A), Overall survival (B).

Table 3. Multivariate analysis of factors predicting for late transplantation outcomes in patients surviving leukemia-free two years after transplantation.

	NRM		Relapse		LFS	
Factor	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Donor (MUD)	1.08 (0.67-1.75)	0.74	0.70 (0.45-1.09)	0.11	0.86 (0.63-1.18)	0.34
Age (per 10 years)	1.56 (1.05-2.32)	0.02	0.95 (0.66-1;38)	0.80	1.26 (0.97-1.63)	0.09
Gender (female)	0.72 (0.49-1.05)	0.09	0.68 (0.48-0.95)	0.02	0.71 (0.55-0.90)	0.006
Donor gender (female)	1.0 (0.68-1.46)	0.99	0.83 (0.58-1.17)	0.28	0.91 (0.71-1.17)	0.46
PBSC vs BM	0.81 (0.45-1.47)	0.49	0.94 (0.56-1.56)	0.80	0.88 (0.60-1.27)	0.49
Cytogenetics						
Intermediate	0.79 (0.36-1.75)	0.56	5.85 (1.41-24.2)	0.01	1.86 (0.96-3.60)	0.07
Poor	1.15 (0.46-2.86)	0.77	7.70 (1.73-34.1)	0.007	2.52 (1.21-5.22)	0.01
missing	0.80 (0.35-1.85)	0.60	5;51 (1.31-23.3)	0.02	1.83 (0.93-3.60)	0.08
CR2 vs CR1	1.02 (0.57-1.83)	0.95	1.93 (1.21-3.08)	0.006	1.51 (1.06-2.16)	0.02
Advanced vs CR1	1.52 (0.92-2.53)	0.10	2.16 (1.39-3.34)	0.006	1.86 (1.36-2.55)	0.0001
RIC vs MAC	0.90 (0.57-1.42)	0.64	1.08 (0.73-1.60)	0.68	0.97 (0.73-1.28)	0.80
T-cell depletion	0.83 (0.54-1.27)	0.38	1.18 (0.81-1.73)	0.37	1.03 (0.78-1.34)	0.85
Year of SCT	1.06 (0.97-1.17)	0.21	0.96 (0.89-1.04)	0.35	1.00 (0.95-1.07)	0.91
Chronic GVHD before 2 years	2.32 (1.50-3.61)	0.0002	0.89 (0.63-1.25)	0.49	1.31 (1.01-1.69)	0.045
Center effect (frailty)		0.12		0.26		0.68

Abbreviations: As in Table 1-2.

Late non-relapse mortality and relapse

The 10-year NRM was 13% (95%CI, 11-16) and 21% (95%CI, 15-28) after matched sibling and MUD transplants, respectively (Fig. 2, P=0.15). NRM was higher in older patients, male patients, patients with advanced leukemia at SCT and patients with prior chronic GVHD (Table 2). Multivariate analysis identified advanced age (HR 1.56 per 10 years, P=0.02) and prior chronic GVHD (HR 2.32, P=0.0002) as independent predicting factors (Table 3). There was no difference in NRM rate between matched sibling and unrelated donors or based on conditioning intensity.

Figure 2

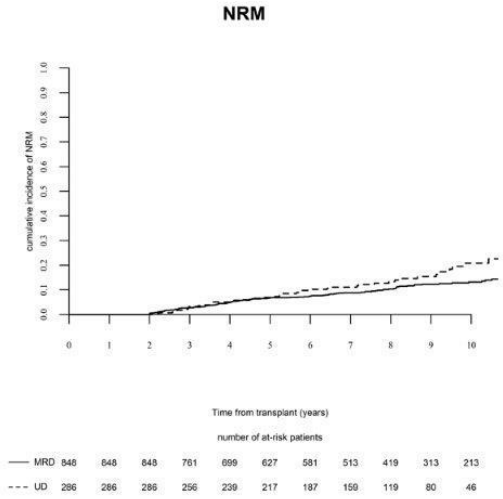

Figure 2. Subsequent non-relapse mortality of patients who were leukemia-free 2 years after stem cell transplantation by donor source.

The 10-year relapse incidence was 15% (95%CI, 13-18) and 17% (95%CI, 12-22) after sibling and MUD transplants, respectively (Figure 3, P=0.97). Multivariate-analysis identified active leukemia at SCT (HR 2.16, P=0.006) or CR2 (HR 1.93, P=0.0006) compared to CR1, intermediate and poor cytogenetics (HR 5.84, P=0.015 and HR 7.70, P=0.007, respectively) and female recipient (HR 0.68, P=0.02) as independent factors predicting late relapse (Table 3). There was no difference in late relapse rate between sibling and unrelated donors or by conditioning intensity. The

occurrence of chronic GVHD prior to the 2-year landmark was not protective of late relapse.

Figure 3.

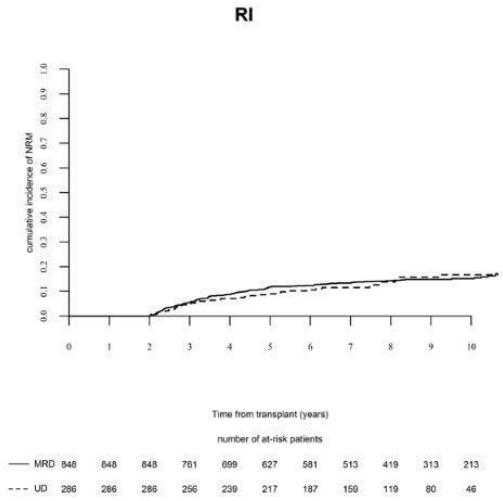

Figure 3. Subsequent relapse rate of patients who were leukemia-free 2 years after stem cell transplantation by donor source.

Late events

There were 209 late deaths after matched sibling transplants and 72 after MUD transplants. Relapse was the leading cause of late death after both regimens. The cumulative incidence of death due to relapse was 12% (95%CI, 10-15) and 10% (95%CI, 6-14), respectively (P=0.24). The cumulative incidence of death due to chronic GVHD was 3% (95%CI, 2-5) and 5% (95%CI, 3-9), respectively (P=0.20) and of the cumulative incidence of death due to infection was 2% (95%CI, 1-4) and 6% (95%CI 3-10), respectively (P=0.05). The cumulative incidence of second malignancies was 8% (95%CI, 6-11) and 10% (95%CI, 6-19), respectively (P=0.67). The 10-year cumulative incidence of death due to second malignancies was 3% (95%CI, 2-5) and 4% (95%CI, 2-9), respectively (P=0.88).

Subgroup analysis

An interaction was found between donor type, conditioning intensity and prior chronic GVHD. SCT outcomes were further assessed in the four subgroups according to this interaction: RIC without prior chronic GVHD, RIC with prior chronic GVHD, MAC without prior chronic GVHD and MAC with prior chronic GVHD. The results are summarized in Table 4. This subgroup analysis showed that in patients who received RIC and had a prior chronic GVHD, LFS was significantly lower in MUD compared to sibling donors (47% vs 70%, P=0.007) due to a higher NRM (33% vs 17%, P=0.006), respectively. Prior chronic GVHD was not a significant factor for NRM and LFS in MAC recipients. However, in patients who received MAC without prior chronic GVHD, LFS tended to be higher after MUD (77% vs 73%, P=0.08).

Table 4: Transplantation outcomes according to subgroup analysis based on conditioning and prior chronic GVHD.

Subgroup		Relapse	NRM	LFS	OS
RIC w/o prior chronic GVHD	Sib (n=178)	20% [14-27]	5 % [2-9]	75% [68-82]	78% [71-84]
	MUD (n=77)	16% [8-26]	9.% [3-19]	75% [63-86]	76% [65-88]
	P value	0.80	0.40	0.76	0.89
RIC with prior chronic GVHD	Sib (n=302)	13% [9-17]	17% [12-22]	70% [64-76]	71% [65-77]
	MUD (n=89)	20% [11-31]	33% [20-47]	47% [32-61]	50% [34-65]
	P value	0.53	0.006	0.007	0.009
MAC w/o prior chronic GVHD	Sib (n=122)	16% [10-23]	12% [7-19]	73% [64-81]	76% [68-84]
	MUD (n=51)	14% [4-29]	10% [2-24]	77% [61-92]	86% [74-98]
	P value	0.32	0.19	0.08	0.04
MAC with prior chronic GVHD	Sib (n=168)	16% [11-22]	17% [11-24]	67% [59-75]	70% [62-78]
	MUD (n=53)	18% [9-31]	18% [8-32]	63% [49-78]	67% [52-81]
	P value	0.61	0.94	0.77	0.94

Abbreviations. As in Table 1-3.

Discussion

The current study shows that with long-term follow-up, LFS is similar after allogeneic SCT from HLA- matched siblings and MUDs in patients with AML, age ≥50 years, who are alive and leukemia-free 2 years after SCT.

Historically, a matched sibling donor was the preferred donor for allogeneic SCT due to the high NRM associated with MUDs. However, with the improved outcome of MUD transplants several studies have shown comparable outcomes in patients with AML.[4,17-25]A large CIBMTR analysis compared the outcome of 2223 adult patients with AML after allogeneic SCT from HLA-matched siblings (n=624), 8/8 matched unrelated (n=1193) and 7/8 matched unrelated (n=406).[24] HLA-matched sibling and 8/8 MUD transplant recipients had similar survival. Mismatched MUD recipients had higher early mortality but their survival beyond 6 months was similar. In all, the 3-year LFS was 35%, 34% and 31%, respectively (P=NS). A more recent EBMT analysis compared 6545 adults patients with AML in high-risk CR1 after allogeneic SCT from sibling (n=3511), 10/10 MUD (n=1959), mismatched MUD (n=549), umbilical cord blood (n=333) or haploidentical donors (n=193).[25] The 2 year OS was similar after matched sibling, MUD and haploidentical transplants (59%, 57% and 57%, respectively), but was inferior after mismatched MUD (49%) and umbilical cord blood donors (49%). In a summary of more than 14,000 patients with AML in different phases of the disease, the average 3-year OS was 47% after matched sibling and 46% after MUD transplants.[4] While, survival rates are approximately the same, MUD recipients have a higher incidence of acute GVHD, and possibly of NRM, especially with mismatched unrelated donors.[24,25] However, relapse rates after SCT may be lower with MUD, and especially mismatched MUD, due to more prominent graft-versus-leukemia effect. This has resulted in an superior outcomes after MUD SCT compared to matched siblings in some reports.[26,27] The excess mortality with mismatched MUD is reduced in more advanced disease phase where patient outcome is mostly dependent on disease control.[5] However, the stronger GVL effect with MUD has been questioned.[28]

These observations are limited to the early-intermediate phases after SCT; the data on the long-term comparison of matched sibling and MUD transplants in patients with AML is limited. Most events after SCT occur within the first 2 years and many of the clinical factors predictive of LFS in the early post-transplant period are no longer predictive later on as the risk for early events declines.[10,12] The largest study of

long-term survival includes 10,632 patients who underwent MAC, and are alive and disease-free at 2 years. In this analysis presented by the CIBMTR, the probability of remaining alive at the 10-year time-point was 85%.[10] Older age and chronic GVHD were risk factors for the population, while advanced disease at SCT was a risk for patients with leukemia. Relapse and NRM occurred in 10% and 9% of AML patients that were alive and disease-free 2 years after SCT.

We have shown that most events after RIC in the matched sibling donor setting also occur in the first 2 years.[12] The 10-year OS of patients alive and disease-free 2 years after SCT was 73% and 74% after MAC and RIC, respectively. Advanced disease at SCT is a significant negative prognostic factor. These rates were mildly lower than those reported in the CIBMTR study, however, the median age of AML patients was 28, with only 6% over age 50 years, while all patients included in the EBMT analysis were over 50 years. In the current analysis we extended the analysis to MUD recipients. We show that the long-term survival is similar for sibling and MUD recipients surviving leukemia-free 2 years after SCT been 74% and 66%, respectively. Similar to the previous reports, the major factor predicting subsequent LFS is disease status at SCT. These data can serve to reassure MUD SCT recipients who reach 2 years that their survival is favorable and not significantly different than recipients of matched sibling SCTs. The causes of subsequent death, however, are different between sibling and MUD recipients. While relapse is the major cause of late death in both, it is a more prominent cause of death after sibling transplants. Infection and chronic GVHD are more prominent causes of late death after MUD. Second malignancies are an important cause of late death, leading to 5-10% of deaths in the large CIBMTR study.[10] In the current analysis in an older patient group, 13% of all late deaths were due to second malignancies, with no difference between sibling and unrelated donor transplants. The surveillance for second cancers remains an important task in long-term patient education and follow-up.[29]

The role of dose intensity in SCT conditioning for AML has been explored in multiple retrospective studies (reviewed in 30). Several retrospective analyses have shown that more intensive regimens control leukemia better, but LFS is not improved due to associated excess NRM.[31-34] More recently, Scott et al, randomized fit patients with AML and MDS with less than 5% blasts to RIC versus MAC.[35] The study was stopped early as relapse rates were markedly higher in the RIC group. The reduction in NRM with RIC was not sufficient to compensate for this elevated risk and LFS was

higher after MAC. The conclusion was that MAC is still the standard regimen for fit patients while RIC can be a suitable alternative in patients who are older or those not eligible for MAC. More recently post-transplant therapies are used including targeted therapies and novel cellular therapies and these may reduce relapse rates after RIC and improve outcome. The median follow-up in this randomized study was 18 months. The current analysis extends these observations to long-term follow-up. The conditioning regimen used did not have an effect on late events in the entire group. However, there were some differences between subgroups, according to the conditioning regimen and occurrence of chronic GVHD prior to the 2-year landmark. Among RIC recipients with chronic GVHD, late outcomes were less favorable in MUD compared to matched sibling donor recipients due to increased NRM. Possibly chronic GVHD has a more adverse prognostic impact in RIC MUD recipients. This effect was not seen in MAC recipients. In these patients chronic GVHD had the same impact after sibling and MUD recipients. In all, both limited and extensive grade of chronic GVHD prior to the 2-year landmark were associated with lower LFS, although this was more pronounced for extensive grade. We found no protective effect of limited GVHD. This possibly relate to a more pronounced effect of chronic GVHD in the first 2 years while those who are leukemia-free at the 2-year landmark do not enjoy further protection from relapse. This finding may also be due to low number of late events when assessing subgroups.

The current retrospective study focused on survival rates. There were no data on performance status and quality of life. GRFS may be a surrogate marker for quality of life and 63% are expected to be GVHD- free and relapse-free at 10 years post-transplant. However, future prospective studies will need to focus also on more formal assessment of quality of life.

In conclusion, long-term outcome is similar after SCT from matched sibling or MUD in older patients with AML. Patients who are leukemia-free 2 years after SCT can expect similar subsequent outcome with both donor types. Disease status was the major predictor of subsequent LFS while conditioning intensity had no effect. While relapse is the major cause of late death after both donor types, NRM and in particular GVHD and infections are more common causes of late death after SCT from MUD.

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