Published in final edited form as:

Biol Blood Marrow Transplant. 2018 June ; 24(6): 1232–1236. doi:10.1016/j.bbmt.2017.09.005.

Haploidentical Transplantation for Older Patients with Acute Myeloid Leukemia and Myelodysplastic Syndrome

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Abstract

Allogeneic stem cell transplant (ASCT) with HLA matched donors is increasingly used for older patients with AML/MDS. It remains unclear if haploidentical transplantation (haploSCT) is a suitable option for older patients with this disease. We analyzed 43 patients with AML/MDS (median age 61 years) who underwent a haploSCT at our institution. All the patients received a fludarabine-melphalan-based reduced-intensity conditioning regimen and post-transplant cyclophosphamide-based GVHD prophylaxis. Except one patient who had early death, the remaining 42 patients (98%) engrafted donor cells. The cumulative incidence (CI) of grade 2–4 and 3–4 acute GVHD (aGVHD) at 6 months was 35% and 5% respectively and chronic GVHD (cGVHD) at 2-years was 9%. After a median follow-up of 19 months, 2-year overall (OS), progression-free survival (PFS), relapse-incidence were 42%, 42%, and 24% respectively. Best

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Authorship contribution

S.O.C. contributed with treatment of the patients, study design, data collection and interpretation and manuscript writing; M.V.S., S.G., P.K. contributed data collection, manuscript writing, reviewed and approved the manuscript; R.M.S. analyzed data, interpreted the results, reviewed and approved the manuscript; G.R. and J.C contributed with data collection, reviewed and approved the manuscript; K.C. contributed with HLA typing, reviewed and approved the manuscript; W.W., M.K., N.D., J.C., F.R., A.A, S.A., U.P., S.P., Q.B., O.B., C.H., E.J.S., K.R., I.F.K., P.K., R.E.C. contributed with treatment of patients, manuscript editing, reviewed and approved the manuscript.

Conflict of interest

The authors have no conflict of interest to declare for this work.

PFS (74% at 2 years) was seen in patients with intermediate/good-risk cytogenetics, in first or second remission (HR:0.4, *P*=0.05) and with a younger donor (≤40 years) (HR=0.2, *P*=0.01).

In conclusion, these data suggest that haploidentical transplantation is safe and effective for older AML/MDS patients. Disease status, cytogenetics, and younger donor age are predictors for improved survival in older patients receiving a haploidentical transplant.

Keywords

haploidentical stem cell transplant; post-transplant cyclophosphamide; elderly patients; acute myeloid leukemia (AML); myelodysplastic syndromes (MDS)

INTRODUCTION

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are diseases of the elderly, with median age at diagnosis into the 7th decade of life.[1,2] Hematopoietic stem cell transplantation (HCT) is an effective treatment for patients with AML/MDS.[3] Our group developed a reduced-intensity conditioning (RIC) regimen with fludarabine-melphalan 140mg/m^2 (FM140) as a potential strategy to decrease transplantation-related mortality (TRM) in older and/or unfit individuals.[4] We have shown that transplantation using this regimen might be an effective treatment for older patients.[5] Since then, FM140 regimen has been increasingly used for HLA-matched transplants. Moreover, our group showed very encouraging results for older individuals with lower melphalan dose (100mg/m^2, FM100).[6,7] A modified version of this regimen, with the addition of thiotepa or 2Gy total body irradiation (TBI), was used for haploidentical transplants (haploSCT) using an unmanipulated bone marrow graft and post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis.[8] In patients with AML/MDS, transplant outcomes after FM-based conditioning regimen were similar between haploidentical- and matched unrelated donors (MUD),[9] findings confirmed in a larger CIBMTR retrospective analysis.[10] In addition, we studied this conditioning regimen prospectively in haploSCT with PTCy and we found similar survival for patients treated with FM100 and FM140 regimen.[11]

In the absence of a suitable sibling donor, haploidentical donors for SCT are increasingly being considered.[12] The use of MUDs is often challenging due to prolonged time to identify and schedule donation, and limited availability for the non-Caucasian population.[13] However, most older patients are not being considered for transplantation, more so with a haploidentical donor, due to concerns of higher TRM, as increasing age is associated with higher comorbidity index, lower performance status, in addition to a higher risk disease, all of which impact survival.[14]

Here we studied outcomes of older patients with AML/MDS patients who underwent a haploidentical transplant at our institution.

MATERIALS AND METHODS

Patients

This retrospective cohort study included all adult patients with AML/MDS above age 55 years who underwent a haploidentical transplant between 06/2009–09/2015. All patients and donors provided written informed consent. Patient demographics and clinical 65 parameters were obtained from medical records. Complete remission (CR) was defined as less than 5% bone marrow blasts with neutrophils $\geq 1\times10^9$/L and platelets $\geq 100\times10^9$/L with or without minimal residual disease. Cytogenetic risk was classified according to the Southwestern Oncology Group (SWOG) risk category.[15] Hematopoietic stem cell transplant comorbidity index (HCT-CI) was assessed as previously described.[16]

The University of Texas MD Anderson Cancer Center Institutional Review Board (IRB) approved this retrospective analysis.

Conditioning Regimen and Supportive Care

All patients received fludarabine (160 mg/m^2 divided in 4 daily doses) and melphalan (100–140 mg/m^2) as a single dose with either thiotepa 5 mg/kg or 2GyTBI. Hematopoietic progenitor cells were obtained from the bone marrow in all cases and infused on Day 0. All patients received PTCy (50 mg/kg/day) on Days +3 and +4 for GVHD prophylaxis, mycophenolate mofetil and tacrolimus starting on Day +5 until Day +100 and after 6 months, respectively, if there was no evidence of GVHD. All patients received standard supportive cares including granulocyte colony–stimulating and antimicrobial prophylaxis as described.[12]

Statistical Analysis

The Kaplan-Meier method was used to estimate actuarial overall survival (OS) and progression-free survival (PFS). NRM, relapse, and GVHD were estimated using the cumulative incidence method to account for competing risks. Predictors of OS were evaluated on univariate and multivariate analysis using Cox proportional hazards regression analysis. Statistical significance was defined at the 0.05 level. Factors that were statistically or clinically relevant on univariate analysis were considered in multivariate analysis. Analyses were performed using STATA 14.0 (College Station, TX, USA).

RESULTS

Patient Characteristics

Clinical characteristics are described in Table 1. Median age at transplant was 61 years (range 55–69). Only 51% of patients were in CR1 or CR2 at the time of transplant. Most (81%) patients had children as donors, while 19% patients received cells from siblings. Median donor age was 37 years (rage 20–62), with 28 (65%) donors being ≤40 years. Most patients received FM100-based regimen (N=29, 67.4%). One patient had early death; the rest engrafted the donor cells. Median time to neutrophil and platelet engraftment was 19 (13–28) and 28 (15–117) days respectively. Day 30 chimerism was 100% donor in 38 (88%) patients.

Transplant outcomes and Factors Affecting Survival

After a median follow-up of 19 months (range 6–49), 20 of 43 patients were alive and in remission. The 2-year overall (OS) and progression-free survival (PFS) for the cohort was 42%, with a relapse incidence of 24%. The 2-year OS, PFS and relapse incidence for patients in CR1/2 versus others were 61% versus 18%, 63% versus 19% and 14% versus 33%, respectively. Non-relapse mortality (NRM) was 21%, 30%, and 34% at day +100, 1- and 2-years respectively. Causes of death were disease recurrence (9 patients), hemorrhage/multiorgan failure (7 patients), infection (3 patients), aGVHD (3 patients) and cGVHD (1 patient). Remarkably, no events were noted after 13 months post-transplant. The cumulative incidence of grade 2–4 and 3–4 aGVHD at 6 months post-transplant was 35% and 5%, respectively, while cGVHD at 2-years post-transplant was 9%.

Next, we evaluated factors influencing outcomes for the cohort. In univariate analysis, disease status at the time of transplant (CR1/2 *vs.* not in CR1/2), donor age (≤40 *vs.*>40 years), and cytogenetic risk at diagnosis (good/intermediate *vs.* poor-risk) were the only factors that predicted survival. None of the other characteristics listed in Table 1 as well as donor/recipient CMV status and ABO matching were significant predictor of OS. The melphalan dose or the use or thiotepa vs. TBI had no impact on outcomes. In multivariate analysis for OS, not in CR1/2 *vs.* CR1/2 (HR 3.3, 95% confidence interval (CI) 1.3–8.1, P=0.01), donor age >40 *vs.* ≤40 years (HR=3.1, 95%CI 1.2–7.7, P=0.01), and poor *vs.* good/intermediate-risk cytogenetics (HR=2.9, 95%CI 1.2–7.2, P=0.02) remained independent predictors for survival (Table 2). Subset analysis showed that the impact of donor age was more pronounced in patients with good/intermediate-risk cytogenetics (HR=4.5, 95%CI 1.3–16, P=0.02) than in patients with poor-risk cytogenetics (HR=1.6, 95%CI 0.3–9.9, P=0.6). The impact of disease status did not differ according to cytogenetics risk group. Age at transplantation had no significant impact on 2-year PFS; however, the PFS at last follow-up appeared to be lower for older age groups trending 46% for patients ≤60 years (reference) to 40% for patients 61–65 years (HR:1.3, CI:0.5–3.1, P=0.6) and 37% for patients >65 years (HR:1.5, CI:0.5–4.3, P=0.5) (Figure 1A). OS at 2-year post-transplant was highest (74%) for patients with good/intermediate-risk cytogenetics who received a graft from a donor age ≤40 years. This effect persisted after adjusting for disease status (Figure 1B).

DISCUSSION

Allogeneic transplantation for older patients with AML/MDS remains a challenge due to the more aggressive nature of the disease in this age group of patients, accumulation of co-morbidities with advancing age and limited HLA-matched related donor availability.[14] However, outcomes for elderly patients in CR1 undergoing RIC SCT are superior compared to those receiving chemotherapy alone.[5] A recent meta-analysis on a larger number of patients concluded that a 35% PFS at 3 years can be expected for patients receiving an HLA matched donor transplant.[17] A prospective study confirmed these findings; thus, transplant consideration is imperative for older patients at least with high-risk AML in CR with lower HCT-CI and good performance status.[18] Unfortunately, less than half of older and otherwise suitable patients have donor available in a timely manner.[5,12] While it is increasingly difficult for older individuals to have an HLA matched related donor, most patients have at

least a child available for transplantation, making haploSCT an attractive immediate option for most patients regardless of race of the recipient.

As compared with 2 prior reports,[19,20] here we evaluated outcomes following haploidentical donor transplants for a homogenous group of older patients with AML/MDS, and found that patients up to the age of 70 years can achieve long-term survival using this approach. Most patients received lower doses of melphalan (100 mg/m2) with no significant difference in survival compared with the more intense conditioning regimen (FM140) (P=0.2), traditionally applied in older individuals. Despite the fact that two thirds of patients in this series had a high HCT-CI ≥3, this regimen was well tolerated with a relatively low NRM for this group of patients. In addition, a remarkable low relapse rate (24% at 2-year) was noted in this cohort, in which half the patients were not in remission at the time of transplant. These results suggest that FM100-based conditioning regimen can be safely applied to older individuals undergoing haploidentical stem cell transplantation with excellent long-term disease control.

Interestingly, results from this study showed that recipient age did not impact post-transplant survival. This might be because of the relatively small number of patients in this report; however, the PFS at last follow-up appeared to be trending up for younger age groups as seen in Figure 1. On the other hand, transplantation using stem cells from younger donors was associated with significant better survival, suggesting that a child should be the preferred donor choice for haploidentical transplants for older individuals.

We should emphasize that, despite the fact that this is the first study evaluating specifically outcomes of older patients with AML/MDS undergoing haploidentical transplantation, this report is retrospective and includes a relatively small numbers of patients. However, we reported outcomes of all patients treated at our institution since this procedure started to be performed eliminating any potential selection bias.

In summary, in this report we evaluated outcomes with haploidentical transplantation in older patients with AML/MDS, and conclude that this approach is safe and effective for this group of patients with remarkable survival for patients up to age 70 years, in morphologic remission at transplant with intermediate/good risk-cytogenetics. Younger donor age was significantly associated with improved survival in these patients, suggesting that children should be the preferred source of stem cells for older patients.

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KEY POINTS

- Haploidentical transplantation with RIC melphalan-based conditioning is safe and effective for older AML/MDS patients.
- Survival was similar for different age groups up to age 70.
- Excellent survival was seen in patients with cytogenetics other then high-risk and a younger donor (≤40 years).
- These results suggest that children should be the preferred donor source for these patients.

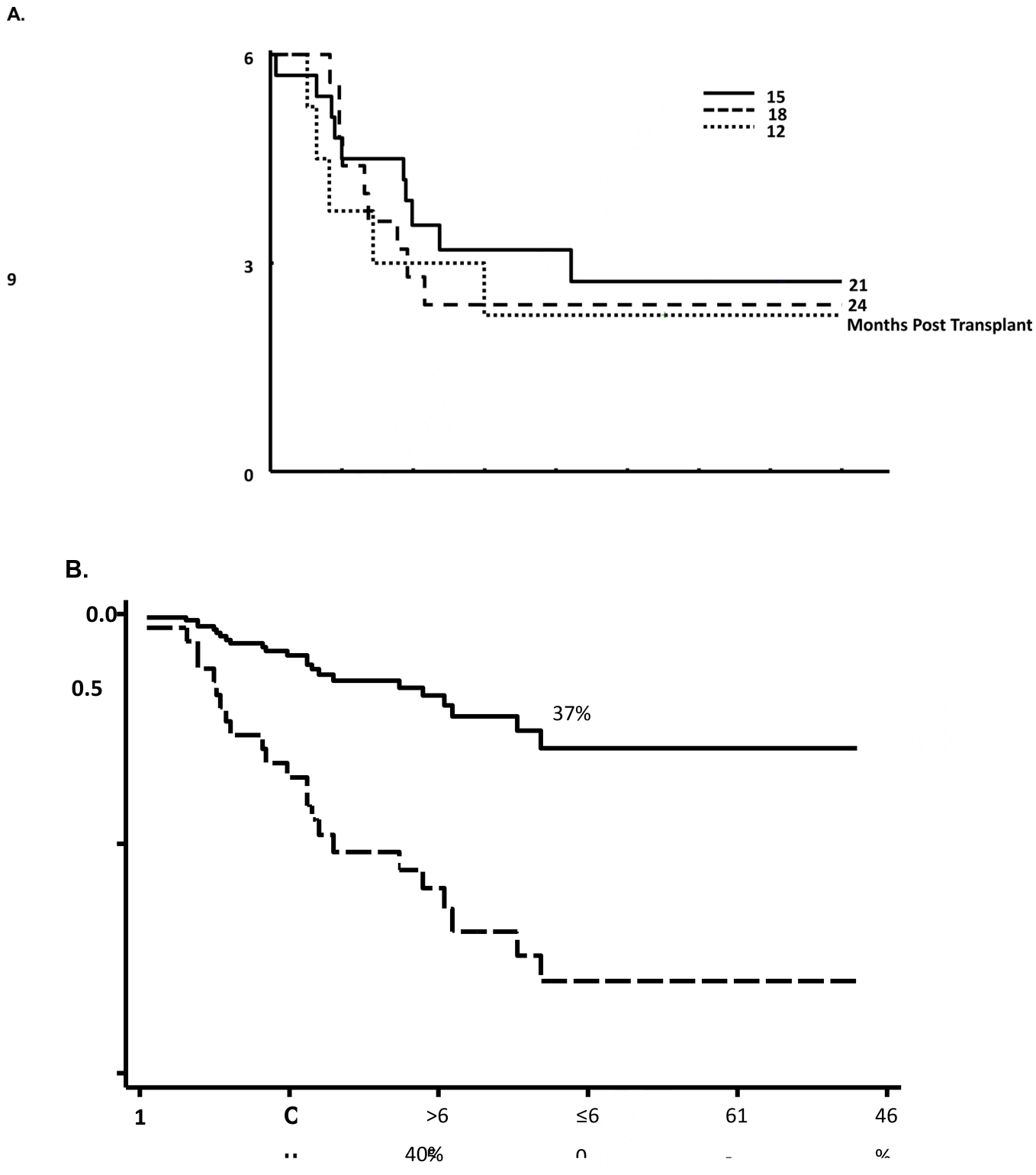

Figure 1.

(A). Progression-free survival based on age groups at transplant **(B).** Patients with good/intermediate-risk cytogenetics at diagnosis and donor age ≤40 years had significantly improved OS compared to patients with poor-risk cytogenetics at diagnosis or donor age >40 years (71% vs. 20%, P=0.006).

Table 1.

Patient, engraftment characteristics and outcomes of elderly patients with AML/MDS undergoing haploidentical transplantation with fludarabine/melphalan-based conditioning.

Characteristic	Value
Age in years, median (range)	61 (55–69)
Follow-up in months in surviving patients, median (range)	19 (6–49)
Disease, N (%)	
AML	25 (58)
MDS	10 (23)
MDS/AML	8 (19)
Cytogenetics at diagnosis, N (%)	
Poor	16 (37)
Intermediate	24 (56)
Good	3 (7)
Conditioning, N (%)	
FM100-based	29 (67)
FM140-based	14 (33)
Stem cell source, N (%)	
BM	42 (98)
Peripheral blood stem cells	1 (2)
Disease status at SCT, N (%)	
CR1 or CR2	22 (51)
Other	21 (49)
HCT-CI score, median (range)	3 (0–11)
Donors' relation to the recipient, N (%)	
Child	8 (19)
Sibling	8 (19)
Donor age in years, median (range)	37 (20–62)
Donor age ≤40 years, N (%)	28 (65)
Sex mismatch, N (%)	
Female donor/Male recipient	6 (14)
Other	37 (29)
Engraftment, N (%) Engrafted	41 (95)
Delayed	1 (2)
Early death	1 (2)
Time to engraftment in days (median, range)	

Characteristic	Value
Time to neutrophil engraftment (n=41)	19 (13–28)
Time to platelet >20,000 (n=31)	28 (15–117)
Outcomes, percent (95% CI)	
2-year OS	42 (26–57)
2-year PFS	42 (27–57)
2-year relapse incidence	24 (14–41)
Day +100 NRM	21 (12–37)
1-year NRM	30 (19–48)
2-year NRM	34 (22–52)
aGVHD maximum grade, N (%)	
0	22 (51%)
1	6 (14%)
2	13 (30%)
3 or 4	2 (5%)
6-month cumulative incidence of aGVHD, percent (95% CI)	
Grade 2–4	35 (23–52)
Grade 3–4	5 (1–19)
Chronic GVHD, N (%)	
de novo	0 (0)
Relapsing	3 (7)
Progressive	0 (0)
2-year cumulative incidence of cGVHD, percent (95% CI)	9 (3–27)

AML – acute myeloid leukemia, MDS – myelodysplastic syndrome, MDS/AML – MDS progressed to AML, Cytogenetics – Southwestern Oncology Group cytogenetics risk category; FM100: fludarabine and melphalan 100 mg/m^2; FM140 – fludarabine and melphalan 140 mg/m^2, BM – bone marrow, CR1 – first complete remission, CR2 – second complete remission, HCT-CI – hematopoietic stem cell transplant comorbidity index; OS – overall survival; PFS – progression free survival; NRM – non-relapse mortality; aGVHD – acute graft-*vs*-host disease; cGVHD – chronic graft-*vs*-host disease.

Table 2.

Predictors of overall survival inmultivariate analysis (Cox).

	HR	95% CI	P value
Disease status not CR1/CR2	3.3	1.3–8.1	0.01
Donor age > 40 years	3.1	1.2–7.7	0.01
Poor-risk cytogenetics	2.9	1.2–7.2	0.02

CR1 – first complete remission; CR2 – second complete remission; CI – confidence interval