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Outcomes of second allogeneic hematopoietic cell transplantation for patients with acute myeloid leukemia

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Abstract

Background: Relapse after allogeneic hematopoietic cell transplantation (HCT) leads to poor survival in patients with acute myeloid leukemia (AML). A second HCT (HCT2) may achieve durable remission.

Objectives: To determine the outcomes of patients who received an HCT2 for relapsed AML and to evaluate the predictors of overall survival (OS) and progression-free survival (PFS).

Study Design: We retrospectively reviewed medical records of adult patients who underwent an HCT2 for relapsed AML at our institution during 2000–2019.

Results: Ninety-one patients were identified with a median age of 44 years (range, 18–73) at HCT2. Donor types were HLA-identical sibling (n=37, 41%), HLA-matched-unrelated (n=34, 37%), haploidentical (n=19, 21%), and cord-blood (n=1, 1%). Donors were different at HCT2 in 53% of patients. The majority of patients received reduced intensity conditioning (n=71, 78%) and were in remission (n=56, 61%) at HCT2. The median remission duration after HCT1 was 8.4 months (range, 1–70) and the median time between transplants was 14 months (range, 3–73). The median follow-up of surviving patients after HCT2 was 66 months (range, 2–171), with 32% alive at time of analysis. The most common cause of death was disease recurrence (n=45, 73%). At 2 years, the rates of OS, PFS, progression, and non-relapse mortality were 36%, 27%, 42%, and 18%, respectively. The development of chronic GVHD after first HCT and HCT comorbidity index (HCT-CI) ≥2 at HCT2 were associated with inferior PFS and OS after HCT2.

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Authorship Contributions

FFY and PK wrote the manuscript. RMS performed statistical analysis. All authors contributed substantially to the conception, acquisition, analysis, and interpretation of the data and approved the final version of the study to be published.

Conflicts of Interest

None of the authors declare any conflicts of interest.

Conclusion: A second HCT is feasible in selected patients with AML who have relapsed after HCT1. Long-term survival benefit is possible in patients without chronic GVHD after HCT1 and HCT-CI <2 at HCT2.

Keywords

Acute myeloid leukemia; second allogeneic stem cell transplantation; survival

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative option for acute myeloid leukemia (AML). Although patients can achieve long-term disease-free remissions after HCT, disease relapse remains a major cause of treatment failure and generally leads to poor survival, with only 10–20% of patients in relapse surviving beyond two years[1]. However, a second HCT can achieve durable remissions in a subset of patients with relapsed AML[2, 3].

Several studies have reported the major predictors of outcome after a second HCT are the duration of remission after first HCT and the status of disease at time of second HCT[4–7]. Age at second HCT, development of graft versus host disease (GVHD) after first HCT, and donor type have also been reported as predictors of outcomes[1, 4, 8, 9]. Notably, these studies included both adult and pediatric patients, included a variety of acute and chronic leukemias, and largely used human leukocyte antigen (HLA)-matched sibling donors. Moreover, they included patients transplanted over a decade ago (Supplemental Table I). Throughout the last decade, donor choice has changed with increased use of HLA-haploidentical donors, more therapeutic agents for relapsed AML have become available, and maintenance therapy following transplant has become more common. Herein, we retrospectively analyzed the outcomes of relapsed AML patients who received a second HCT at our institution within the last two decades and additionally sought to investigate any potential impact of time-period on transplant outcomes.

Materials and Methods

Patient and study design

The University of Texas MD Anderson Cancer Center Institutional Review Board approved this retrospective analysis. All patients provided written informed consent for transplantation in accordance with the Declaration of Helsinki. Adult patients ≥ 18 years of age who received a second HCT for relapsed AML from January 1, 2000 until August 1, 2019 were identified through a retrospective review of our clinical database. All relevant demographic, clinical, laboratory and pathologic data were retrospectively abstracted.

Definitions and clinical end points

AML was diagnosed according to the 2016 World Health Organization (WHO) criteria for hematological malignancies[10]. Cytogenetic risk stratification was based on the 2017 European LeukemiaNet (ELN) guidelines[11]. The response assessment was based on the revised criteria defined by the International Working Group for AML[12].

Haploidentical donors were defined as having two or more mismatches from a related donor. Myeloablative (MAC) and reduced intensity conditioning regimens (RIC) were defined according to the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria[13]. Acute GVHD was staged and graded according to the criteria published by Przepiorka et al[14]. Chronic GVHD was reported as limited and/or extensive based on the criteria published by Sullivan et al[15].

Evaluation of outcomes and statistical analysis

The primary outcome of interest was overall survival (OS), defined by the time from second HCT to death or last known follow-up. Secondary outcomes included cumulative incidence of progression, progression free survival (PFS), defined as disease progression or death following the second HCT, non-relapse mortality (NRM), defined as death without recurrent or progressive disease after second HCT, and acute and chronic GVHD. Actuarial OS and PFS were estimated using the Kaplan-Meier method. Observations were censored at the time of last follow-up or third HCT (n=3), when applicable. The cumulative incidence of disease progression, NRM, and GVHD were estimated to account for competing risks. Univariate analyses were performed for PFS, OS, NRM and progression; multivariate analyses were performed for OS and PFS using Cox proportional hazard models. Backward elimination was used to develop multivariate prognostic models. First degree interaction effects were evaluated and accounted for in the regression analysis, as indicated. Characteristics were compared using Chi-square and Fisher's exact tests for categorical variables, and Wilcoxon's rank-sum test was used for continuous variables. Statistical significance was defined at the .05 level and statistical analyses were primarily performed using Stata 9.0 (College Station, TX).

Results

Patient characteristics at second HCT

A total of 91 patients were included in this study. Each received an HCT for AML and subsequently received a second HCT for relapsed disease from January 2000 through August 2019 at our institution (Supplemental Figure 1). Patient, disease, and transplant characteristics at time of first and second HCT are presented in Table I. The median age at time of second HCT was 43 years (range, 18–73 years) and 48 (53%) of the patients were male. Fifty-six patients (61%) were in complete remission (CR) with or without hematologic recovery (CRi) at the time of second HCT, whereas 22 (24%) were transplanted with active disease. A total of 13 (14%) patients had either aplastic marrow (n=8, 9%) or received salvage treatment following the most recent marrow evaluation, precluding disease evaluation (n=5, 5%). The HCT comorbidity index (HCT-CI) was 2 or higher in approximately half of the patients. The median remission duration after the first HCT was 8.4 months (range, 1–70 months) and patients proceeded to a second HCT at a median of 14 months (range, 3–73 months) following the first HCT.

Transplant characteristics at second HCT

The majority of patients (78%) received a RIC regimen consisting largely of melphalan (100–140 mg/m^2) as a single dose with fludarabine (40 mg/m^2) given for 4 days (n=59) or

intravenous busulfan at a fixed dose of 100 mg/m^2 or targeting an area under the concentration versus time curve (AUC) of 4,000 μMol-min ±10% (n=3). Twenty patients (22%) received a MAC preparative regimen consisting of intravenous busulfan either at a dose calculated to target an AUC of 5,000–6,000 μMol-min ±10%, or 130 mg/m^2 in combination with fludarabine (40 mg/m^2) given daily for 4 days.

Forty-eight (53%) patients switched to a different donor for the second HCT (Table I). Most donors were matched siblings (41%) or matched (9/10 or 10/10) unrelated donors (37%). The majority of mismatched donors were haploidentical (21% of the total patient population). The primary donor source was peripheral blood stem cells (78%), followed by bone marrow (21%) and cord blood (1%). GVHD prophylaxis was primarily (n=85, 97%) tacrolimus-based. In addition, one-third (n=25, 28%) of the patients received post-transplant cyclophosphamide prophylaxis. A median of 4 cycles (range, 1–12) of maintenance therapy following transplant was administered in 14% of patients, which consisted mainly of azacitidine (32 mg/m^2/day) subcutaneously for 5 days every 28 days (n=11) or sorafenib (n=2).

A comparison of patient, disease, and transplant characteristics between the previous (2000–2010) and more recent decade (2011–2019) is shown in Table II. Notably, no patients with active disease were transplanted in the recent decade, compared with 22 (48%) who were transplanted with active disease during the previous decade. Furthermore, in the recent decade a different donor was selected more frequently (67% vs 39%; p=0.008), haploidentical donors were used more often (38% vs 4%, p=0.0002), and more patients received maintenance therapy (27% vs 2%, p=0.0007).

Study outcomes

Following the second HCT, 85 patients (93%) engrafted. Among these, all achieved neutrophil engraftment and 68 (80%) achieved platelet engraftment at a median of 12 days (range, 9–40 days) and 14 days (range, 8–54), respectively. The cumulative incidence of day 28 neutrophil and platelet engraftment was 99% and 65%, respectively. The cumulative incidence of grades 3–4 acute GVHD at 100 days was 11% (95% CI 6–20%) and the cumulative incidence of chronic GVHD at 2 years was 18% (95% CI 10–32%).

A total of 29 patients (32%) were alive at the time of this analysis. The median follow-up among survivors was 66 months (range, 2–171 months) and median OS was 11 months. Forty patients (44%) had disease relapse/progression at a median of 6 months after the second HCT (range, 1–86 months) and 17 patients experienced NRM. The cumulative incidence of progression and NRM at 2 years was 42% (95 CI 32–54) and 18% (95% CI 12–28%), respectively. OS and PFS at 2 years were 36% (95% CI 26–47%) and 27% (95% CI 18–37%), respectively (Figure 1). Causes of death were disease recurrence (n=45, 73%), infections (n=6, 10%), GVHD (n=4, 6%), and other causes of NRM (n=7, 11%).

Through our univariate analysis (Table III), we found that HCT-CI ≥2 and development of chronic GVHD after first HCT were associated with significantly inferior PFS and OS following the second HCT. The only significant univariable covariate for NRM was older

age (>60 years) and none of the covariates were associated with significant disease progression.

Evaluation of the predictors of OS and PFS stratified by decade was also completed through univariate analysis (data not shown). This analysis revealed a significant (p=0.04) interaction effect for the impact of the duration of remission after first HCT on OS. We found that a short (≤ 6 months) remission duration after the first HCT was associated with worse OS in the more recent (HR=2.5, 95% CI 1.1–5.5, p=0.03), but not in the previous (HR=0.8, 95% CI 0.4–1.7, p=0.5) decade. There were no interaction effects associated with PFS. Because of the skewed distribution by decade of remission status and donor type, we performed subset analyses to evaluate the impact of each factor within the relevant time period. Consistent with results for the overall cohort, there was no association with OS or PFS for either factor.

In the multivariate analysis (Table IV), we found that inferior OS after the second HCT was associated with chronic GVHD after the first HCT (HR 2.9 (95% CI, 1.5–5.7; p=0.001)), HCT-CI ≥2 at second HCT (HR 2.6 (95% CI, 1.4–4.9; p=0.003)), relapse within 6 months of first HCT (limited to patients who received a second HCT between 2011 and 2019) (HR 2.6 (95% CI, 1.1–5.8; p=0.02)), and second HCT before 2011 (limited to patients with >6 months remission duration after first HCT) (HR 2.5 (95% CI, 1.2–5.2; p=0.02)). Among these, development of chronic GVHD after first HCT (HR 3.4 (95% CI, 1.8–6.4; p <0.001)) and HCT-CI ≥2 (HR 2.1 (95% CI, 1.2–3.7; p=0.01)) were also significantly associated with worse PFS.

Discussion

In this study, we retrospectively analyzed the outcomes of adult patients who underwent a second HCT for relapsed AML over the last two decades at our institution and investigated the impact of time on our management and outcomes.

In our study, 36% of the patients were alive 2 years after their second HCT and 27% were relapse free, while 20% died from NRM. These results are in line with previous studies that demonstrated comparable OS and PFS following second HCT[8, 16, 17]. Furthermore, patients who received a second HCT in the recent decade, and particularly those who had a long remission after their first HCT, demonstrated substantial improvement in overall survival compared to those who underwent transplantation in the prior decade (Figure 2). These results support previously published findings[18].

Identifying prognostic factors associated with survival after second HCTs informs clinicians on the potential benefit of recommending a second HCT in relapsed AML. Published retrospective studies demonstrated that the biological aggressiveness of the underlying leukemia, as reflected by the duration of remission after first HCT and ability to achieve a remission prior to second HCT, were important predictors of outcomes after second HCT[4, 5, 19]. Consistent with published data, we confirmed a significant association between survival and the time from first HCT to relapse. Perhaps due to small sample size, we did not

find a statistically significant association between persistence of disease at time of second transplant and transplant outcomes.

We also found that the occurrence of chronic GVHD after the first HCT was an unfavorable predictive factor for overall and progression free survival after the second HCT. These findings agree with a recent study by Ruutu et al., who completed a retrospective registry analysis of 2632 patients with various relapsed hematologic malignancies and found that chronic GVHD after first HCT was an adverse prognostic factor following the second HCT[9]. The study also reported higher NRM and lower OS after second HCT in patients who developed chronic GVHD after first HCT. However, not all studies reported a similar effect of chronic GVHD, and some have even reported beneficial effects of chronic GVHD in reducing relapse after second HCT[8]. Further studies are needed to clarify this interaction.

Remarkably, advanced age as a dichotomized variable was not a significant predictor detected through our univariate analysis, though there was a trend towards inferior outcomes. In general, age is a commonly used prognostic parameter in transplantation. However, a more thorough classification of patients under the aspect of prognosis was demonstrated by including parameters like physical capacity, nutritional status, and comorbidities in several studies of hematological malignancies[20]. The HCT-CI was developed to better define and assess pre-existing comorbidities in hematological malignancies[21]. It is widely used and is predictive of survival in transplant recipients[22]. In the present study, an increased comorbidity burden (HCT-CI ≥2) was an independent predictor of clinical outcomes, which is in line with results from previous studies conducted in HCT recipients[23, 24]. To the best of our knowledge, this is the first study reporting the relevance of HCT-CI as a poor prognosticator in the setting of second HCT in relapsed AML.

Another factor that has been reported to impact the outcome after second HCT is the development of grade 3–4 acute GVHD after first HCT[25]. In our cohort, only four patients with a history of acute GVHD underwent a second HCT and we identified a statistically insignificant trend towards inferior survival in these patients. The prognostic impact of other factors such as donor sex, conditioning regimen and graft source are unclear, and we did not find any impact of these factors on subsequent survival after second HCT. Importantly, changing donors for the second transplant was also not beneficial, corroborating an earlier CIBMTR and more recent European Group for Blood and Marrow Transplant analyses[5, 6, 9]. Furthermore, although recent data has shown a benefit for using HLA-haploidentical donors in patients with relapsed leukemia after a first HCT[26, 27], we failed to show better outcomes. These findings are in line with the EBMT registry analysis[16].

Our analysis has several limitations including its retrospective nature with its inherent biases. Similar to previous studies, ours is limited by its relatively small sample size and by the heterogeneity of the transplant regimens used. Additionally, most patients in our study did not have molecular mutations evaluable at time of second HCT, which may impact prognosis[28].

In summary, a second transplant may be beneficial in a select group of patients. Careful consideration of patient characteristics and review of outcomes after the first transplant can be used to inform decision making regarding the completion of second HCTs in patients with AML.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. Second hematopoietic stem cell transplants may be beneficial for select AML cases.
2. GVHD and HCT-CI ≥2 were associated with worse outcomes after a second transplant.
3. Donor change or using a haploidentical donor does not affect outcomes.

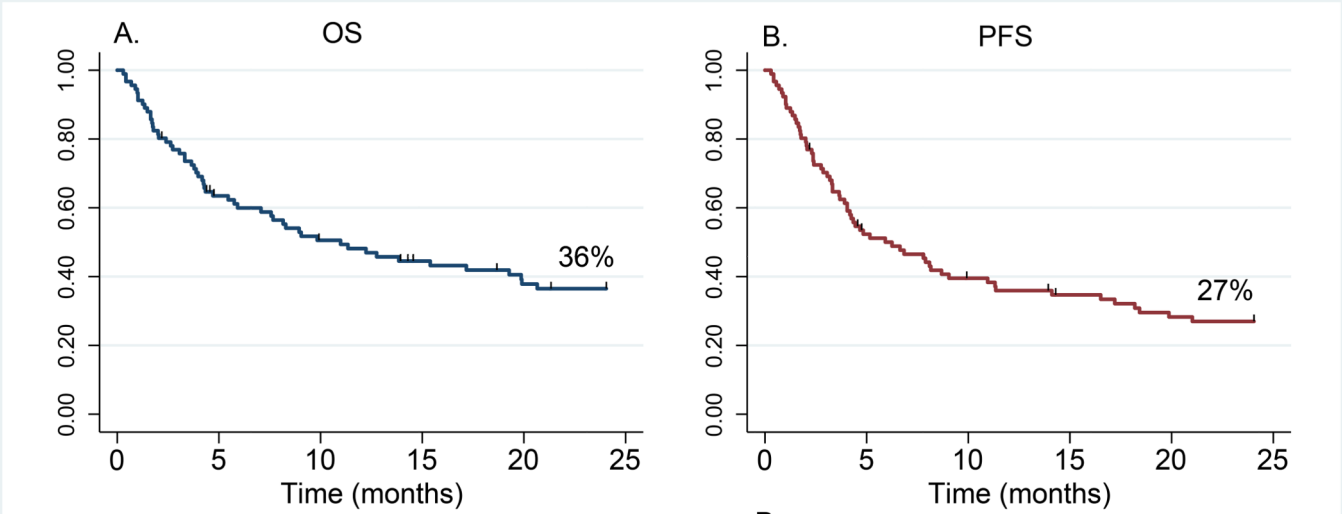

Figure 1.

Overall (left) and progression-free (right) survival of patients who received second HCT. OS=Overall Survival; PFS=Progression-Free Survival.

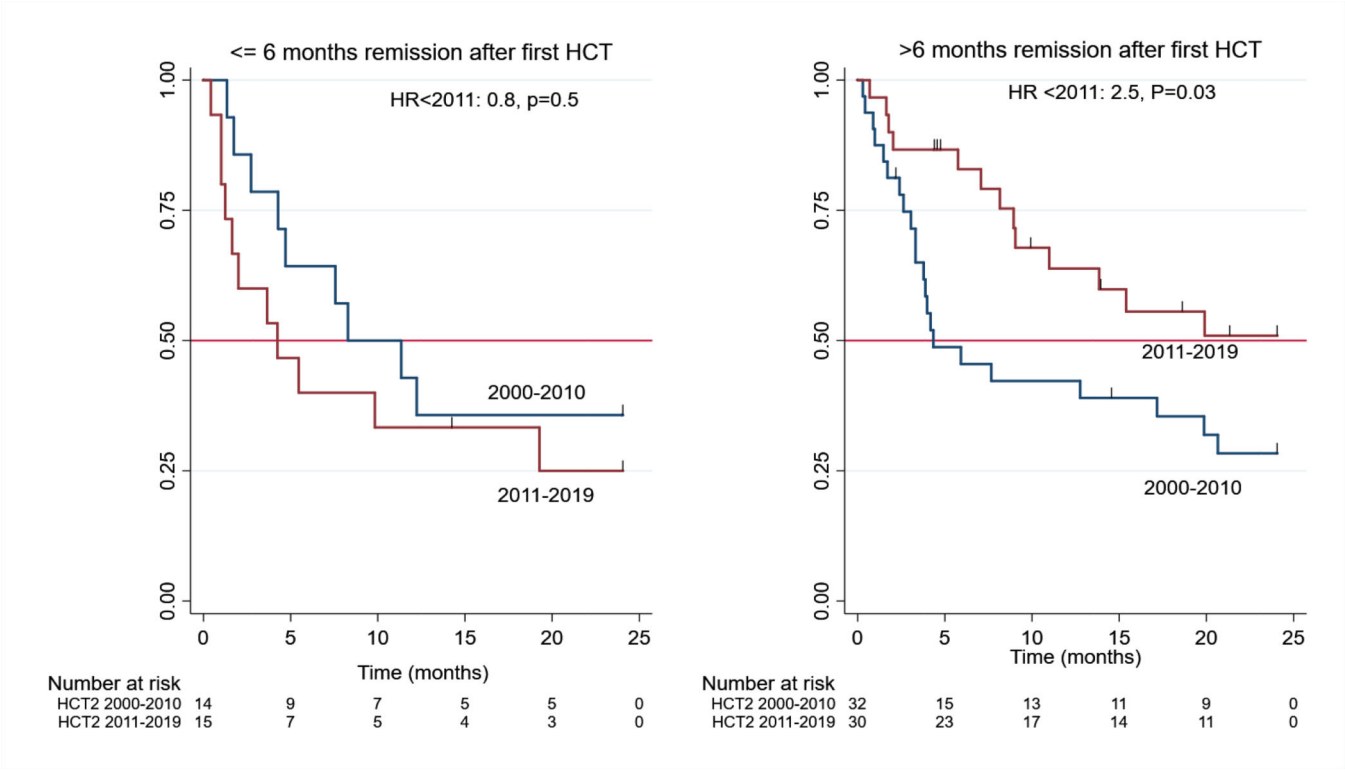

Figure 2.

Overall survival of patients who received second HCT ≤ 6 months (left) or > 6 months (right) after first HCT, stratified by decade second HCT was received.

Table I.

Baseline patient and transplant characteristics, N=91.

Variables	First HCT, N (%)	Second HCT, N (%)
Median age at HCT in years (range)	43 (18–67)	44 (18–73)
Males	55 (60)	48 (53)
Disease status at HCT		
CR/CRi	58 (64)	56 (61)
Persistent disease	29 (32)	22 (24)
Unevaluable *	4 (4)	13 (15)
HCT Comorbidity index		
0–1	-	45 (49)
≥2	-	46 (51)
Remission duration of first HCT, months (range)	8.4 (1–70)	NA
Median time from first to second HCT, months (range)	NA	14 (3–73)
Change in donors	NA	48 (53)
Median calendar year of HCT (range)	2009 (2000–2018)	2010 (2000–2019)
Conditioning intensity		
MAC (Bu>4000)	61 (67)	20 (22)
RIC/NMA	30 (33)	71 (78)
Bu<4000	5 (5)	3 (3)
Mel	23 (25)	59 (65)
100	4 (4)	16 (18)
140	19 (21)	43 (47)
Other	2 (3)	9 (10)
Graft source		
Peripheral blood	51 (56)	71 (78)
Bone marrow	34 (37)	19 (21)
Umbilical cord blood	6 (7)	1 (1)
Donor relation		

Variables	First HCT, N (%)	Second HCT, N (%)
Mismatched unrelated (cord)	6 (7)	1 (1)
Matched sibling donor	42 (46)	37 (41)
10/10 Matched unrelated donor	33 (36)	32 (35)
9/10 Matched unrelated donor	4 (4)	2 (2)
Mismatched family (haploidentical)	6 (7)	19 (21)
GVHD prophylaxis		
Tacrolimus + MTX	75 (82)	63 (69)
PTCy +/− Tacrolimus +/− MMF	15 (17)	25 (28)
Other	1 (1)	3 (3)
Acute GVHD	39 (43)	44 (48)
Grade 2–4	18 (20)	32 (35)
Grade 3–4	4 (4)	13 (14)
Chronic GVHD	17 (19)**	25 (27)

Abbreviations: HCT=hematopoietic cell transplantation; CR=complete response; CRi=complete response with incomplete hematologic recovery; MAC=myeloablative conditioning; RIC=reduced intensity conditioning; NMA=non-myeloablative conditioning; BU=busulfan; Mel=melphalan; GVHD=graft-versus-host disease; MTX=methotrexate; MMF=mycophenolate mofetil; PTCy=posttransplant cyclophosphamide.

*Includes patients with 1) aplastic marrow insufficient for analysis and/or 2) patients who received a salvage treatment following the most recent disease evaluation.

**Includes 9 patients with limited and 8 patients with extensive chronic GVHD.

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Table II.

Comparison of disease and transplant characteristics between the last two decades.

Variables	Second HCT between 2000–2010 N=46 (100%)	Second HCT between 2011 and 2019 N=45 (100%)	p value
Age at AML diagnosis, median (range)	41 (18–67)	43 (17–66)	0.47
Males, n (%)	23 (50)	25 (56)	0.67
Therapy related disease, n (%)	3 (6)	3 (6)	1.00
Cytogenetic risk at diagnosis (per ELN)			0.44
Favorable	2 (5)	3 (7)	
Intermediate	27 (64)	22 (50)	
Adverse	13 (31)	19 (43)	
Not evaluable	4	1	
Cytogenetic risk at time of second HCT (per ELN)			0.78
Favorable	0	0	
Intermediate	30 (75)	31 (79)	
Adverse	10 (25)	8 (21)	
Not evaluable	6	6	
Age at second HCT, median(range)	43.5 (18–68)	47 (21–73)	0.39
Duration of remission after first HCT, months, median (range)	8 (1–49)	9 (1–71)	0.61
≤6 months	14 (30)	15 (33)	0.8
>6 months	32 (70)	30 (67)	
Median time from relapse to second HCT, months (range)	3.1 (0.3–31)	4.1 (2–40)	**0.01**
Median time from first to second HCT, months (range)	12.1 (2.6–51.5)	14.9 (6.5–74.2)	0.15

Variables	Second HCT between 2000–2010 N=46 (100%)	Second HCT between 2011 and 2019 N=45 (100%)	p value
Salvage treatment after relapse following first HCT, n (%)	35 (76)	44 (98)	**0.003**
High dose cytarabine based	26 (57)	21 (47)	
High dose cytarabine based plus DLI	1 (2)	2 (5)	
Hypomethylating-based	6 (13)	15 (33)	
Hypomethylating-based plus DLI	1 (2)	6 (13)	
DLI only	1 (2)	0	
None	11 (24)	1 (2)	
Remission status at second HCT			**<.0001**
CR/CRi	20 (43)	36 (80)	
Persistent disease	22 (48)	0	
Unevaluable*	4 (9)	9 (20)	
MRD status a second HCT			
Positive	1 (5)	8 (22)	
Negative	4 (20)	19 (53)	
Not evaluable	15 (75)	9 (25)	
HCT Comorbidity index			0.21
0–1	26 (57)	19 (42)	
≥2	20 (43)	26 (58)	
Donor selection			**0.008**
Same donor	28 (61)	15 (33)	

Variables	Second HCT between 2000–2010 N=46 (100%)	Second HCT between 2011 and 2019 N=45 (100%)	p value
Different donor	18 (39)	30 (67)	
Donor relation			**0.0002**
Umbilical cord	0	1 (2)	
Matched sibling	26 (57)	11 (24)	
Matched unrelated (9/10, 10/10)	18 (37)	16 (33)	
Mismatched family (haploidentical)	2 (4)	17 (38)	
Graft type			0.44
Peripheral blood	37 (80)	34 (76)	
Bone marrow	8 (18)	11 (24)	
Umbilical cord blood	1 (2)	0	
Conditioning intensity			1.00
MAC (Bu>4000)	10 (22)	10 (22)	
RIC/NMA	36 (78)	35 (78)	
Maintenance following second HCT, n (%)	1 (2)	12 (27)	**0.0007**
HMA based maintenance	1 (2)	9 (20)	
Targeted maintenance	0	3 (7)	
None	45 (98)	33 (73)	

Abbreviations: HCT=hematopoietic cell transplantation; AML=acute myeloid leukemia; ELN=European Leukemia Network; CR=complete response; CRi=complete response with incomplete hematologic recovery; MAC=myeloablative conditioning; RIC=reduced intensity conditioning; NMA=non-myeloablative conditioning; BU=busulfan; Mel=melphalan; HMA=hypomethylating agent.

*Includes patients with 1) aplastic marrow insufficient for analysis and/or 2) patients who received a salvage treatment following the most recent disease evaluation.

Table III.

Univariate analysis of factors for outcomes after second HCT

Variables		Progression Free Survival		Overall Survival		Progression		Non Relapse Mortality	
	N vs N	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Second HCT before vs after 2011	46 vs 45	1.4 (0.8–2.4)	0.2	1.2(0.75–2.02)	0.4	0.9 (0.4–1.6)	0.6	1.1 (0.4–2.8)	0.9
Age at second HCT ≥60 vs <60 years	16 vs 75	1.5 (0.7–3.6)	0.3	1.5 (0.7–3.3)	0.3	0.9 (0.3–2.9)	0.8	3.8 (1.2–12)	**0.02**
Age at second HCT ≥40 vs <40 years	54 vs 37	1.7 (0.96–2.9)	0.07	1.5 (0.9–2.5)	0.09	1.4 (0.7–2.6)	0.4	1.4 (0.5–3.7)	0.5
Female vs Male	43 vs 48	1.5 (0.9–2.6)	0.1	1.2 (0.7–1.9)	0.5	0.8 (0.4–1.6)	0.5	0.9 (0.3–2.4)	0.8
HCT-CI ≥2 vs 0–1	46 vs 45	1.8 (1.0–3.2)	**0.05**	1.7 (0.99–2.9)	**0.05**	1.01 (0.5–1.9)	0.9	1.3 (0.5–3.4)	0.6
Primary vs t-AML	85 vs 6	1.7 (0.7–4.3)	0.3	1.9 (0.8–4.4)	0.1	1.4 (0.4–4.6)	0.6	0.9 (0.1–5.6)	0.9
Response before second HCT									
CR/CRi vs Persistent disease*	56 vs 22	0.8 (0.4–1.5)	0.5	0.7 (0.4–1.2)	0.2	0.6 (0.3–1.2)	0.1	1.5 (0.4–5.4)	0.5
Duration of remission after first HCT									
≤6 months vs >6 months	28 vs 63	1.4 (0.8–2.4)	0.3	1.4 (0.8–2.4)	0.2	0.6 (0.3–1.2)	0.1	1.5 (0.4–5.4)	0.5
Haploidentical vs another donor	19 vs 72	0.8 (0.4–1.6)	0.5	0.86 (0.5–1.6)	0.6	0.8 (0.4–1.7)	0.6	0.9 (0.2–3.2)	0.9
Haploidentical vs MUD or MRD	19 vs 32 / 37	0.8 (0.4–1.6)	0.5	0.9 (0.5–1.6)	0.7	0.8 (0.4–1.7)	0.6	0.9 (0.3–3.3)	0.9
MUD vs MRD	32 vs 37	0.7 (0.4–1.4)	0.3	0.8 (0.5–1.5)	0.5	0.9 (0.5–1.9)	0.9	2.5 (0.7–8.2)	0.1
Same vs different donor	43 vs 48	0.9 (0.5–1.5)	0.7	0.8 (0.5–1.3)	0.3	1.1 (0.6–2.2)	0.7	0.5 (0.2–1.4)	0.2
MAC vs RIC for second HCT	20 vs 71	1.1 (0.6–2.1)	0.6	1.3 (0.7–2.3)	0.4	1.2 (0.6–2.6)	0.6	1.1 (0.4–3.4)	0.8
Graft source									
Peripheral blood	71	1.0 (0.6–1.8)	0.9	0.8 (0.4–1.6)	0.6	1.6 (0.7–3.6)	0.3	0.6 (0.2–1.7)	0.3
Bone marrow	19	Ref.		Ref.		Ref.		Ref.	
Cord blood	1	Ref.		Ref.		Ref.		Ref.	
GVHD prophylaxis for second HCT									
PTCy vs no PTCy	25 vs 66	0.6 (0.3–1.2)	0.2	0.7 (0.4–1.2)	0.2	0.8 (0.3–1.6)	0.4	0.6 (0.2–2.2)	0.5
Acute GVHD grade 3–4 after first HCT	4 vs 87	2.8 (0.9–9)	0.09	2.2 (0.7–6.9)	0.2	0.9 (0.4–2.2)	0.9	1.7 (0.2–15)	0.6
Chronic GVHD after first HCT	17 vs 74	3.03 (1.7–5.5)	**<0.001**	2.6 (1.5–4.8)	**0.001**	0.9 (0.4–2.4)	0.9	1.7 (0.5–5.2)	0.4
Cytogenetic risk per ELN at time of second HCT									
Adverse vs intermediate	18 vs 61	1.3 (0.7–2.3)	0.4	0.9	0.4	2.0 (0.9–4.2)	0.06	0.5 (0.1–2.5)	0.4

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Abbreviations: HCT=hematopoietic cell transplantation; HR=hazards ratio; MRD=measurable residual disease; CI=confidence interval; t-AML=therapy related acute myeloid leukemia; CR=complete response; CRi=complete response with incomplete hematologic recovery; MRD=matched related donor; MUD=matched unrelated donor; CB=cord blood; MAC=myeloablative conditioning; RIC=reduced intensity conditioning; ELN=European Leukemia Network; GVHD=graft-versus-host disease; PTCy=posttransplant cyclophosphamide.

*Unevaluable patients excluded (unevaluable include patients with 1) aplastic marrow insufficient for analysis and/or 2) patients who received a salvage treatment following the most recent disease evaluation.

Table IV.

Multivariate analysis of factors for progression-free and overall survival after second HCT.

Variables	Progression Free Survival			Overall Survival		
	HR	95% CI	p value	HR	95% CI	p value
History of cGVHD after first HCT	3.4	1.8–6.4	<0.001	2.9	1.5–5.7	0.001
HCT-CI≥2	2.1	1.2–3.7	0.01	2.6	1.4–4.9	0.003
≤6 months remission after first HCT	1.2	0.7–2.2	0.4	2.6*	1.1–5.8	0.02
Second HCT before 2011	1.2	0.7–1.9	0.5	2.4*	1.1–5.1	0.02

Abbreviations: HCT=hematopoietic cell transplantation; HR=hazards ratio; CI=confidence interval; cGVHD=chronic graft-versus-host disease; HCT-CI=hematopoietic cell transplantation comorbidity index; NS=not significant.

*Hazard ratios reflect adjustment for a significant interaction effect between transplant decade and duration of remission of first transplant.