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Transplant Outcomes for Secondary Acute Myeloid Leukemia: Acute Leukemia Working Party of the European Society for Blood and Bone Marrow Transplantation Study

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A B S T R A C T

Secondary acute myeloid leukemia (sAML) has been associated with inferior outcomes compared with de novo AML. Little is known about patient risk factors and outcomes in sAML after allogeneic hematopoietic stem cell transplantation (HCT); thus, this large systemic analysis of the European Society for Blood and Bone Marrow Transplantation registry was performed. This study included 4997 patients with sAML who received HCT from 2000 to 2016. In univariate analysis the 2-year cumulative incidence of chronic graft-versus-host disease (GVHD), relapse, and nonrelapse mortality (NRM) were 33.5% (95% confidence interval [CI], 32% to 34.9%), 33.7% (95% CI, 32.3% to 35.1%), and 27.5% (95% CI, 26.1% to 28.7%), respectively. Overall survival (OS), leukemia-free survival (LFS), and GVHD-free, relapse-free survival (GRFS) at 2 years were 44.5% (95% CI, 43% to 46%), 38.8% (95% CI, 37.4% to 40.3%), and 27.2% (95% CI, 25.9% to 28.6%), respectively. In multivariate analysis, patients receiving myeloablative regimens had decreased relapse (hazard ratio, .859; 95% CI, .761 to .97; $P = .01$), higher NRM (hazard ratio, 1.175; 95% CI, 1.03 to 1.341; $P = .02$), and no differences in OS, LFS, and GRFS compared with patients receiving reduced-intensity conditioning regimens. Active disease, adverse cytogenetics, older age, Karnofsky performance status (≤80%), ex vivo T cell depletion, other malignant hematologic diseases, and patient cytomegalovirus seropositivity were associated with inferior OS and LFS. These variables should be considered in patients with sAML in need of HCT, and further study regarding the impact of conditioning regimens on relapse is needed.

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INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease that remains challenging to treat, regardless of whether it occurs de novo or secondary to an antecedent malignancy or its treatment. Hematopoietic stem cell transplantation (HCT) is the postremission treatment of choice in high-risk AML patients. It is unclear what percentage of all cases of AML are due to secondary AML (sAML) because of poor reporting, undiagnosed antecedent myelodysplastic syndrome (MDS), and exclusion from most clinical trials. However, it is believed that sAML comprises a significant proportion of all cases of AML and constitutes a high-risk subtype [1-3].

The World Health Organization has historically defined sAML as AML that occurs with an antecedent myeloid disease such as MDS or a myeloproliferative neoplasm (MPN) regardless of prior therapy. Therapy-related AML is defined as AML that has occurred as a complication of prior cytotoxic chemotherapy or radiation therapy for either a solid tumor or hematologic malignancy [4]. Studies in the past have combined these 2 categories as sAML [3,5-7], and both categories have been shown to have inferior outcomes compared with de novo AML [1,8-10]. Data have shown that this is in part due to the higher frequency of adverse molecular mutations and high-risk cytogenetic abnormalities such as *TP53* in patients with sAML, particularly in patients with therapy-related AML [11-14]. Furthermore, these patients also tend to be of older age at diagnosis, have had more preceding treatment, and also are more likely to have a poor response to standard intensive chemotherapy. However, it remains unclear if it is sAML itself that is an independent poor prognostic factor despite the aforementioned variables [8,9,15-17].

Some population-based studies have shown that patients with an antecedent hematologic disease, particularly that of non-MDS AML, tend to have poorer outcomes, particularly younger patients. Ostgardt et al. [18] reported in their national population-based study that patients with an antecedent myeloid disorder or prior cytotoxic exposure had decreased complete remission (CR) rates and poorer overall survival (OS) after intensive therapy. Increased age and adverse cytogenetics were also critical determinants of outcomes, except in patients who had non-MDS AML, in which outcomes were dismal despite taking into account age and cytogenetics [1,18].

Although these prognostic factors are known in patients with sAML who undergo initial chemotherapy, what remains unclear is how these variables affect outcomes as they relate to patients who ultimately undergo HCT—likely the only potentially curative treatment for this disease. Risk factors and outcomes based on the antecedent disease and other pretransplant factors after allogenic HCT are largely unknown. Therefore, the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Bone Marrow Transplantation (EBMT) performed the largest registry study to date on patients with sAML undergoing HCT to study this further.

METHODS

Study Design and Data Collection

We used the EBMT registry to identify 4997 patients with a diagnosis of sAML who received HCT between 2000 and 2016 in this retrospective multicenter analysis. Data were provided by the ALWP of the EBMT group registry. The EBMT registry is a voluntary working group of more than 500 transplant centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. The audits are routinely performed to determine the accuracy of the data. Since 1990, patients have provided informed consent authorizing the use of their personal information for research purposes. The study was approved by the general assembly of ALWP.

Eligibility criteria for this analysis included adult patients (ages > 18 years) with a diagnosis of sAML. Patients with sAML were defined as patients diagnosed with AML who had an antecedent MDS, MPN, overlap MDS/MPN, other malignant hematologic disorder (OMHD), bone marrow failure syndrome, or solid tumor with prior chemotherapy or radiation therapy. Variables collected included recipient and donor characteristics (age, gender, cytomegalovirus [CMV] serostatus), disease features, previous diagnosis (MDS/MPN, OMHD, bone marrow failure syndrome, solid tumor), cytogenetics (favorable, intermediate, adverse), Karnofsky performance status (KPS) at transplant, disease status at transplant (first CR [CR1] versus CR2/3 versus active disease [≥5% blasts in bone marrow]), transplant-related factors including conditioning regimen (myeloablative conditioning [MAC] or reduced-intensity conditioning [RIC]), donor type (matched sibling donor, unrelated donor, other relative [haploidentical], or cord blood transplant [CBT]), degree of match (10/10, 9/10, or haploidentical), immunosuppression (in vivo T cell depletion [TCD] versus none), graft-versus-host-disease (GVHD) prophylaxis, and outcome variables (acute and chronic GVHD [aGVHD, cGVHD], relapse, nonrelapse mortality [NRM], leukemia-free survival [LFS], OS, and causes of death).

Statistical Analysis

The primary endpoint of the study was OS and LFS. Secondary endpoints included disease relapse incidence, NRM, engraftment, incidences and severity of aGVHD and cGVHD, and GVHD-free, relapse-free survival (GRFS). The starting point for time-to-event analysis was date of transplantation. OS was defined as the time to death from any cause. LFS was defined as survival without relapse or progression. Patients surviving were censored at time of last follow-up. Relapse incidence was defined as time to onset of leukemic recurrence. NRM, defined as death without relapse or progression, was the competing risk, and patients surviving in continuous CR were censored at last contact.

Cumulative incidence curves were used for relapse incidence and NRM in a competing risk setting, because death and relapse are competing. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan-Meier method. Cumulative incidence was used to estimate the endpoints of NRM, relapse incidence, aGVHD, and cGVHD to accommodate competing risks. To study aGVHD and cGVHD, we considered relapse and death to be competing events. Univariate analyses were done using the Gray's test for cumulative incidence functions and the log rank test for OS, GRFS, and LFS. A Cox proportional hazards model was used for multivariate regression on all patients except AML secondary to bone marrow failure syndrome because of a low number of patients. All variables associated with one outcome in univariate analysis were included in the Cox model.

Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). Proportional hazards assumptions were checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All tests were 2-sided. The Type I error rate was fixed at .05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS 24.0 (SPSS Inc, Chicago, IL) and R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria [https://www.R-project.org/]).

RESULTS

Patient, Disease, and Transplant Characteristics

Details of patient, disease, and transplant characteristics are summarized in Tables 1 and 2. Included in this study were 4997 patients with sAML who underwent HCT between 2000 and 2016. Most patients had a prior diagnosis of MDS/MPN (3960, including 663 MPN), OMHD (467, including 73 patients with acute leukemia, 56 with chronic leukemia, 318 with lymphomas, and 20 with plasma cell disorders), solid tumor (537, including 324 patients with breast cancer), or bone marrow failure syndrome, predominantly severe aplastic anemia (33). Median age at time of HCT was 58 years (interquartile range, 50 to 64). Median time from diagnosis to HCT was 4.62 months (interquartile range, 3.18 to 6.89). Median follow-up of surviving patients was 27 months (interquartile range, 7.35 to 60.63).

At the time of transplantation, 2625 patients (52.5%) were in CR1, 290 (8.2%) were in CR2 or beyond, and 2082 patients (41.7%) had active disease. Medical Research Council cytogenetic classification data at the time of diagnosis of sAML were available in 2016 patients (40%; favorable, 74; intermediate, 1255; adverse, 687). One thousand nine hundred

Table 1
Patient, Disease, and Transplant Characteristics

Characteristic	Value	Percentage
Age at transplant, yr		
Median	58.07	
Range	18.11-79.26	
IQR	49.71-63.99	
Year of transplant	2011	
Median		
Range	2000-2016	
Time diagnosis to transplant, mo		
Median	4.62	
Range	1.5-200	
IQR	3.18-6.89	
Donor age, yr		
Median	42	
Range	10-79	
IQR	28-50.91	
Previous diagnosis		79.25
MDS/MPN	3960	
OMHD	467	9.35
Solid tumor	537	10.75
BMFS	33	.66
Status at transplant		52.53
CR1	2625	
CR2/3	290	5.8
Active disease	2082	41.66
Donor		30.96
MSD	1547	
URD	2957	59.18
Haploidentical	320	6.4
CBT	173	3.46
Cytogenetics		1.48
Favorable	74	
Intermediate	1255	25.12
Adverse	687	13.75
KPS at transplant		8.52
KPS < 80%	388	
KPS ≥ 80%	4165	91.48
Conditioning regimen		39.67
MAC	1976	
RIC	3005	60.33
GVHD prophylaxis		18.89
CSA	881	
CSA+MTX	1529	32.79
CSA+MMF	1504	32.25
CSA+MTX+MMF	55	1.18
Tacro+Siro	39	.84
MMF+Tacro	155	3.32
MTX+Tacro	85	1.82
PTCY	212	4.55
Other	203	4.35
Patient CMV serology		33.23
CMV negative	1526	
CMV positive	3066	66.77
Donor CMV serology		50.38
CMV negative	2294	
CMV positive	2259	49.62
aGVHD		72.31
No GVHD to grade II	3440	
Grades II-IV	1317	27.69
Missing	240	
Engraftment		5.52
Graft failure	244	
Engrafted	4176	94.48

Missing data: donor age, 2179; cytogenetics NA/failed, 2981 (59.6%); KPS, 444; conditioning regimen, 16; GVHD prophylaxis, 334; patient CMV serology, 405; donor CMV serology, 444; aGVHD, 240; engraftment, 577. IQR indicates interquartile range; BMFS, bone marrow failure syndrome; CSA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; Tacro, tacrolimus; Siro, sirolimus; PTCY, post-transplant cyclophosphamide.

seventy-six patients (39.7%) received MAC regimens and 3005 patients (60.3%) RIC regimens (missing = 16). The most commonly used MAC regimens included total body irradiation (n = 528), busulfan-cyclophosphamide (n = 452), and busulfan-fludarabine (n = 383), whereas the most common RIC regimens were busulfan-fludarabine (n = 899), fludarabine-melphalan (n = 619), and total body irradiation (n = 563).

Donor sources were matched sibling donor in 1532 patients (41.7%), unrelated donor (9/10 or 10/10) in 2957 patients (59.2%), other relative (haploidentical) in 320 patients (6.4%), and CB in 173 (3.5%). Female donor for male recipients were used in 875 cases (17.7%), and 1097 patient–donor pairs (24.4%) were CMV negative pre-HCT.

All patients received calcineurin inhibitor–based GVHD prophylaxis, and 2988 (63.9%) received in vivo TCD (most rabbit antithymocyte globulin). Most patients had a KPS of 80% or greater (4165, 91.5%) at the time of transplant. CMV status is outlined in Table 1. Myeloid engraftment occurred in most patients who underwent HCT (4176, 94.5%); 244 (5.5%) had graft failure with no difference in incidence based on disease type (MDS/MPN versus solid tumor versus OMHD; $P = .2$) or donor type with the exception of patients who received CBT ($P < .0001$). Grades II to IV aGVHD by day 100 was seen in 1317 patients (28%; 95% CI, 26.8% to 29.3%), whereas cumulative incidence of grades III to IV aGVHD by day 100 was 11.8% of patients (95% CI, 10.9% to 12.8%).

Toxicity and NRM

Overall transplant outcomes are shown in Table 3. The 2-year cumulative incidence of NRM was 27.4% (95% CI, 26.1% to 28.7%) (Figure 1, Table 4). The major causes of NRM were infection and GVHD, which occurred in 615 (24.4%) and 414 (15.5%) of patients, respectively. Death from organ toxicity such as cardiac toxicity, veno-occlusive disease, and bleeding complications was very low, at approximately 1% each. Other causes of death are outlined in Table 4. In multivariable analysis, factors associated with higher NRM included patients transplanted with active disease (HR, 1.58; 95% CI, 1.38 to 1.79); patients with OMHD (HR, 1.31; 95% CI, 1.05 to 1.63) compared with prior diagnosis of MDS/MPN; older age (HR per 10 years, 1.20; 95% CI, 1.12 to 1.27); adverse cytogenetics (HR, 1.87; 95% CI, 1.00 to 3.46); patients who received MAC (HR, 1.17; 95% CI, 1.03 to 1.34); patients transplanted from unrelated donor (HR, 1.44; 95% CI, 1.22 to 1.69), other relative (HR, 1.68; 95% CI, 1.31 to 2.17), or CBT (HR, 1.94; 95% CI, 1.37 to 2.75) compared with matched sibling donor; patient CMV seropositivity (HR, 1.25; 95% CI, 1.09 to 1.43); and those who received ex vivo TCD (HR, 1.66; 95% CI, 1.2 to 2.28). Female gender and good KPS > 80% were associated with a lower NRM (HR, .84; 95% CI, .74 to .96; and HR, .59; 95% CI, .60 to .78, respectively). Factors that did not appear to impact NRM were donor gender and donor CMV seropositivity (Table 6).

Relapse

The 2-year cumulative incidence of relapse was 33.7% (95% CI, 32.3 to 35.1) (Figure 1, Table 5). In multivariate analysis the incidence of relapse was significantly higher in patients who were transplanted with active disease (HR, 1.67; 95% CI, 1.48 to 1.87), had adverse cytogenetics (HR, 2.41; 95% CI, 1.44 to 4.04), and underwent ex vivo TCD (HR, 1.45; 95% CI, 1.07 to 1.98). Patients who had good KPS > 80% (HR, .79; 95% CI, .65 to .95), received MAC and who underwent transplantation from an unrelated donor had decreased risk of relapse post-HCT. There was no difference in relapse risk among patients with prior MDS/MPN, OMHD, or solid tumors (Table 6).

Table 2
Patient and Transplant Characteristics by Disease Type

	MDS (n = 3297)	MPN (n = 663)	Lymphoma (n = 318)	OMHD (n = 149)	ST (n = 537)	BMFS (n = 33)
Median age at treatment	59	59.8	49.4	53.8	53.5	45.5
Range	(18.1-79.3)	(22.1-75.4)	(18.3-75.9)	(18.4-71.8)	(18.8-76)	(21-65.6)
IQR	(51.2-64.5)	(53.9-65.2)	(38.8-59.5)	(39.6-61)	(46.2-60.6)	(36.4-53.7)
Median year of treatment	2011	2012	2010.5	2011	2010	2009
Range	(2000-2016)	(2000-2016)	(2000-2016)	(2000-2016)	(2000-2016)	(2001-2015)
Median time of previous diagnosis to treatment, mo	7	12	60.5	60.8	43	105
Range	(1-390.5)	(1-438.1)	(1-498.1)	(1-438.6)	(1-475.6)	(4.4-318.6)
IQR	(2.8-16.1)	(4.4-33.8)	(29.8-111.7)	(32.9-100.5)	(24.9-76.8)	(59.9-158.7)
Sex						
Male	2002 (60.78%)	434 (65.46%)	179 (56.29%)	100 (67.11%)	109 (20.3%)	21 (63.64%)
Female	1292 (39.22%)	229 (34.54%)	139 (43.71%)	49 (32.89%)	428 (79.7%)	12 (36.36%)
Missing	3	0	0	0	0	0
Cytogenetics						
Favorable	9 (.94%)	0 (0%)	15 (7.32%)	3 (2.91%)	47 (10.28%)	0 (0%)
Intermediate	623 (65.24%)	197 (72.43%)	102 (49.76%)	62 (60.19%)	259 (56.67%)	12 (50%)
Adverse	323 (33.82%)	75 (27.57%)	88 (42.93%)	38 (36.89%)	151 (33.04%)	12 (50%)
NA/Failed	2342	391	113	46	80	9
Donor type						
Matched sibling	971 (29.45%)	193 (29.11%)	122 (38.36%)	39 (26.17%)	212 (39.48%)	10 (30.3%)
Unrelated	2020 (61.27%)	410 (61.84%)	164 (51.57%)	86 (57.72%)	259 (48.23%)	18 (54.55%)
Haploidentical	204 (6.19%)	46 (6.94%)	20 (6.29%)	15 (10.07%)	33 (6.15%)	2 (6.06%)
CBT	102 (3.09%)	14 (2.11%)	12 (3.77%)	9 (6.04%)	33 (6.15%)	3 (9.09%)

LFS and OS

The 2-year cumulative incidence of LFS in this cohort was 38.8% (95% CI, 37.4% to 40.3%) (Figure 1, Table 4). In multivariable analysis, LFS was significantly lower for patients who were transplanted with active disease (HR, 1.63; 95% CI, 1.49 to 1.77), those with older age (HR, 1.08; 95% CI, 1.04 to 1.13), adverse cytogenetics (HR, 2.15; 95% CI, 1.45 to 3.20), those who underwent ex vivo TCD (HR, 1.54; 95% CI, 1.23 to 1.92), and those with OMHD (HR, 1.17; 95% CI, 1.01 to 1.35). Results of multivariate analysis of LFS are summarized in Table 6. As expected, patients with better KPS had better LFS.

Table 3
Overall Transplant Outcomes

Outcome	Percentage	95% CI
2-Year LFS	38.8	37.4-40.3
2-Year OS	44.5	43-46
2-Year relapse incidence	33.7	32.3-35.1
2-Year NRM	27.4	26.1-28.7
aGVHD grades II-IV (100 day)	28	26.8-29.3
aGVHD grades III-IV (100 day)	11.8	10.9-12.8
2-Year chronic GVHD	33.5	32-34.9
2-Year extensive chronic GVHD	15	13.9-16.1
2-Year GRFS	27.2	25.9-28.6

Table 4
Causes of Death

Cause of Death	No. of Patients	Percentage
Relapse	1240	46.5
Infection	651	24.4
GVHD	414	15.5
Other treatment related	153	5.7
Interstitial pneumonitis	49	1.8
Veno-occlusive Disease	45	1.7
Second malignancy	43	1.6
Hemorrhage	31	1.2
Cardiac toxicity	29	1.1
Failure/rejection	11	.4

Missing: n = 197.

The OS of the entire cohort at 2 years was 44.5% (95% CI, 43% to 46%) (Figure 1, Table 4). Multivariable analysis showed lower OS for patients who were transplanted in CR2 or with active disease (HR, 1.23; 95% CI, 1.02 to 1.49; and HR, 1.61; 95%, CI 1.47 to 1.76, respectively). In terms of disease types, patients who had OMHD also had poorer OS (HR, 1.20; 95% CI, 1.03 to 1.39). As expected, patients with adverse cytogenetics had also significantly worse OS (HR, 2.28; 95% CI, 1.49 to 3.50). Other transplant-related factors with inferior survival outcomes included older patients, those patients who underwent transplant with a CBT or a haploidentical donor, patients with CMV seropositivity, and those who underwent ex vivo TCD. There was no difference in LFS or OS in patients who received RIC regimens compared with those who received MAC regimens. Results of multivariable analysis of OS are summarized in Table 6.

In summary, active disease, adverse cytogenetics, older age, KPS (≤80%), ex vivo TCD, OMHD and patient CMV seropositivity were the variables associated with inferior OS and LFS. Receipt of a haploidentical transplant or CBT was associated with lower OS but was not significant for LFS (Table 6).

Graft-versus-Host Disease

The 2-year cumulative incidence of cGVHD was 33.5% (95% CI, 13.9% to 16.1%), with incidence of extensive cGVHD at 15% (95% CI, 13.9% to 16.1%). Univariate analysis of GVHD is summarized in Table 7. Two-year GRFS was 27.2% (95% CI, 25.9% to 28.6%).

In multivariable analysis, factors that were associated with significantly increased risk of grades II to IV aGVHD were active disease at transplant (HR, 1.31; 95% CI, 1.15 to 1.49), use of an unrelated donor (HR, 1.47; 95% CI, 1.26 to 1.72) or CBT (HR, 1.49; 95% CI, 1.03 to 2.16), and use of MAC regimens (HR, 1.23; 95% CI, 1.08 to 1.41) (Table 8). Women and patients who underwent in vivo TCD had lower risk of grades II to IV aGVHD (HR, .86; 95% CI, .76 to .98; and HR, .71; 95% CI, .62 to .82, respectively). In terms of risk of cGVHD, active disease (HR, 1.19; 95% CI, 1.05 to 1.36) and donor female versus male were the only 2 variables with statistically significant

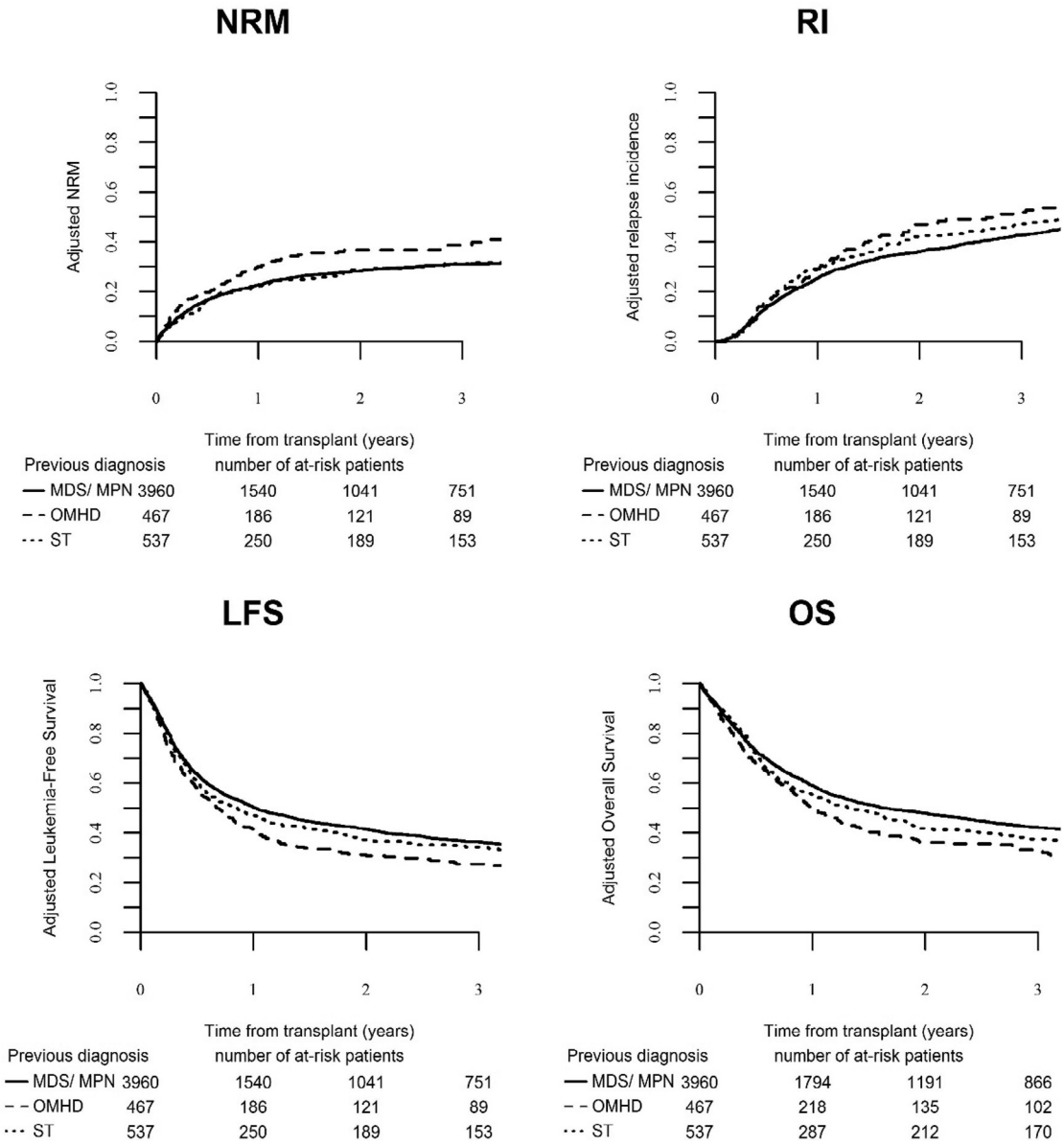

Figure 1. Transplant outcomes based on disease type before developing sAML.

adverse impact in this cohort. Patients who underwent CBT and in vivo TCD were noted to have a lower risk of cGVHD (HR, .43; 95% CI, .27 to .69; and HR, .63; 95% CI, .55 to .73, respectively) (Table 7). For GRFS in multivariate analysis, patients who were transplanted beyond CR1 had poorer outcomes (CR2: HR, 1.22; 95% CI, 1.03 to 1.44; CR3: HR, 1.55; 95% CI, 1.43 to 1.68), whereas adverse cytogenetics, older age, poorer KPS, and female donor were all also associated with inferior GRFS. History of in vivo TCD was associated with a higher GRFS. Multivariable analysis of GVHD-related outcomes are summarized in Table 8.

DISCUSSION

AML remains a therapeutic challenge, particularly in patients with sAML. Consensus remains that allogeneic transplantation remains the best treatment option for patients with high-risk AML after intensive therapy, although specific outcomes for patients with sAML with HCT remain largely unknown. What is known in the literature is that patients with sAML, if treated conservatively, have a poorer prognosis than patients with de novo AML [8,19-23]. This present study is a large registry study retrospectively evaluating allogeneic transplantation outcomes in 4997 patients with sAML, including patients with an antecedent hematologic malignancy or patients with treatment-related disease, within the EBMT registry. To our knowledge, this is the largest registry study in patients with sAML undergoing transplantation to date.

OS, LFS, and GRFS at 2 years were 44.5% (95% CI, 43% to 46%), 38.8% (95% CI, 37.4% to 40.3%), and 27.2% (95% CI, 25.9% to 28.6%), respectively, which is in line with reported data on survival outcomes for patients after allogeneic transplantation for AML [24]. However, multivariate analysis showed that those patients in our cohort who underwent MAC had lower incidences of relapses, but this was at the cost of higher NRM with no associated differences in survival outcomes.

Table 5
Univariate Analysis of Relapse, NRM, LFS, OS, and GRFS at 2 Years

		2 Years				
		Relapse	NRM	LFS	OS	GRFS
Diagnosis	MDS	32.1% [30.4-33.8]	28% [26.4-29.6]	40% [38.1-41.8]	45.6% [43.8-47.5]	28.3% [26.6-30]
	MPN	41.4% [37.4-45.4]	28.4% [24.8-32.1]	30.2% [26.3-34]	36.9% [32.7-41]	18.9% [15.5-22.2]
	Lymphoma	36.7% [31.2-42.3]	31.6% [26.3-37]	31.5% [26-37]	38.1% [32.3-43.9]	22.4% [17.4-27.4]
	OMHD	32.6% [24.8-40.5]	24.7% [17.9-32.2]	42.7% [34.3-51.1]	45.7% [37.1-54.2]	32.2% [24.2-40.3]
	Solid tumor	34.1% [30-38.3]	21.6% [18.1-25.3]	44.2% [39.8-48.6]	49.1% [44.7-53.6]	31% [26.8-35.1]
	BMFS	18.2% [7.2-33.1]	30.3% [15.6-46.4]	51.5% [34.5-68.6]	53% [35.5-70.4]	37.5% [20.7-54.3]
	P value	.14787	.011271	.002938	.0050347	.0087063
If MDS or MPN	MDS (n = 3258)	31.9% [30.2-33.6]	28% [26.4-29.6]	40.1% [38.3-41.9]	45.7% [43.9-47.6]	28.4% [26.7-30.1]
	MPN n = (663)	41.4% [37.4-45.4]	28.4% [24.8-32.1]	30.2% [26.3-34]	36.9% [32.7-41]	18.9% [15.5-22.2]
	P value	2.6285e-06	.95726	1.5865e-06	3.598e-05	3.9211e-06
If solid tumor	Other solid tumor (n = 213)	32.7% [26.3-39.3]	22.1% [16.6-28.1]	45% [38-52]	49.4% [42.3-56.5]	33.3% [26.5-40]
	Breast cancer (n = 324)	35% [29.7-40.4]	21.2% [16.8-26]	43.7% [38-49.3]	49% [43.3-54.7]	29.5% [24.2-34.7]
	P value	.51523	.69031	.71704	.78656	.49289
Status at transplant	CR1	30.4% [28.5-32.3]	23.2% [21.4-24.9]	46.4% [44.4-48.5]	52.3% [50.2-54.4]	33.8% [31.8-35.8]
	CR2/3	33.2% [27.4-39.1]	26% [20.8-31.6]	40.5% [34.3-46.7]	47.4% [41.1-53.7]	27.9% [22.3-33.5]
	Active disease	37.8% [35.7-40]	33% [30.9-35.1]	29.2% [27.1-31.3]	34.5% [32.3-36.7]	19.1% [17.3-20.9]
	P value	4.3669e-07	1.3878e-14	1.2997e-46	1.0328e-43	1.1814e-41
Donor Type	MSD	39.3% [36.7-41.8]	20.2% [18.1-22.3]	40.5% [37.9-43.1]	46.6% [43.9-49.3]	26.1% [23.7-28.4]
	UD 10/10	29.2% [26.6-31.8]	27.3% [24.8-29.8]	43.5% [40.6-46.4]	49% [46.1-51.9]	31.8% [29.1-34.6]
	UD 9/10	30.2% [25.5-35]	35.7% [30.8-40.7]	34.1% [29.1-39]	39.4% [34.3-44.6]	24.7% [20.1-29.3]
	Haploidentical	31.8% [26.4-37.5]	36% [30.5-41.6]	32.1% [26.5-37.8]	36.8% [30.9-42.7]	24.5% [19.3-29.7]
	CBT	30.1% [23.3-37.3]	37.3% [29.9-44.6]	32.6% [25.4-39.8]	35.8% [28.4-43.2]	24.2% [17.6-30.9]
	P value	6.5137e-09	5.5067e-14	.0071672	1.7164e-05	.076925

Values are HRs with 95% CIs in brackets. MSD indicates matched sibling donor; UD, unrelated donor.

Although specific disease types had no effect on relapse incidence, having a prior hematologic malignancy other than an MDS/MPN was independently shown to affect NRM and poorer survival. As expected, certain patient variables such as having active disease before transplant, adverse cytogenetics, older age, poor KPS, and CMV seropositivity were associated with poorer survival outcomes as well. Patients who needed alternative donor transplants such as from CB or a haploidentical donor also had inferior outcomes in this study, although the numbers of those transplants were low.

Relapse after allogeneic transplantation for treatment of AML remains a challenge, accounting for approximately 40% of cases of treatment failure, and is the major cause of treatment failure after transplant [25]. Survival after post-transplant relapse is dismal, with less than 20% survival at 2 years postrelapse. Our study showed a cumulative incidence

Table 6
Multivariate Analysis of Relapse, NRM, LFS, and OS

	Relapse			NRM			LFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
CR1 (reference)												
CR2/3	1.104	.83-1.469	.49563	1.157	.852-1.571	.34939	1.134	.921-1.397	.23493	1.191	.961-1.478	.11109
Active disease	1.728	1.516-1.97	<10-5	1.429	1.228-1.663	<10-5	1.595	1.445-1.761	<10-5	1.544	1.392-1.712	<10-5
MDS (reference)												
MPN	1.499	1.266-1.774	<10-5	1.024	.83-1.263	.82416	1.28	1.123-1.46	.00022	1.234	1.075-1.417	.0029
Lymphoma	1.2	.924-1.559	.17244	1.557	1.175-2.064	.00206	1.353	1.117-1.639	.00198	1.328	1.087-1.624	.00561
OMHD	1.079	.733-1.587	.70126	1.043	.683-1.594	.84501	1.056	.794-1.405	.70935	1.071	.796-1.441	.6521
Solid tumor	1.165	.938-1.447	.16679	.921	.7-1.211	.55502	1.069	.903-1.267	.43708	1.067	.894-1.273	.47357
BMFS	.441	.164-1.185	.10434	.428	.137-1.342	.14563	.441	.209-.931	.03164	.488	.231-1.031	.05998
Age (per 10 yr)	1.017	.958-1.08	.57554	1.238	1.148-1.334	<10-5	1.103	1.053-1.156	4e-05	1.125	1.071-1.182	<10-5
Good risk cytogenetics (reference)												
Intermediate risk	1.193	.7-2.034	.51656	1.68	.851-3.315	.13488	1.362	.896-2.069	.14834	1.386	.887-2.167	.15213
Adverse risk	2.309	1.35-3.949	.00225	2.102	1.055-4.184	.03455	2.202	1.443-3.359	.00025	2.249	1.433-3.527	.00042
NA/failed	1.454	.851-2.486	.1708	1.723	.87-3.41	.11858	1.549	1.017-2.359	.0414	1.626	1.039-2.547	.0335
KPS > 80%	.854	.689-1.059	.15006	.546	.441-.677	<10-5	.691	.594-.804	<10-5	.646	.552-.755	<10-5
MSD (reference)												
UD 10/10	.667	.573-.777	<10-5	1.295	1.076-1.559	.00622	.874	.778-.982	.02386	.981	.867-1.109	.75359
UD 9/10	.759	.612-.941	.01172	1.714	1.357-2.166	1e-05	1.07	.915-1.251	.39699	1.239	1.052-1.458	.01015
Haploidentical	.84	.641-1.099	.20333	1.622	1.228-2.144	.00067	1.11	.916-1.344	.28829	1.274	1.046-1.552	.01612
CBT	.811	.565-1.165	.25634	1.94	1.37-2.745	.00019	1.182	.922-1.516	.18699	1.292	1-1.669	.04961
Patient female vs. male	1.069	.939-1.216	.31324	.813	.699-.947	.00759	.949	.86-1.047	.29463	.917	.827-1.016	.09847
Donor female vs. male	.881	.773-1.003	.05582	1.091	.939-1.266	.25572	.963	.873-1.062	.45069	1.002	.904-1.11	.96839
MAC vs. RIC	.85	.74-.976	.02114	1.219	1.045-1.422	.01154	.993	.896-1.101	.89856	1.009	.906-1.124	.87287
Patient CMV positive	1	.871-1.148	.99682	1.217	1.035-1.432	.01779	1.09	.981-1.21	.10961	1.117	1-1.249	.0496
Donor CMV positive	1.023	.896-1.167	.74104	.952	.819-1.105	.51514	.989	.896-1.092	.8302	1.016	.916-1.127	.76436
In vivo TCD	1.109	.963-1.277	.15175	.984	.837-1.156	.84434	1.054	.948-1.173	.32863	.986	.882-1.102	.80596
Ex vivo TCD	1.384	.947-2.022	.09329	1.93	1.337-2.787	.00045	1.612	1.239-2.098	.00038	1.634	1.249-2.136	.00034

Table 7
Univariate Analysis of GVHD

		100 Days		2 Years	
		aGVHD Grades II-IV	aGVHD Grades III-IV	cGVHD	Extensive cGVHD
Diagnosis	MDS	27.6% [26-29.2]	12.1% [11-13.3]	34.8% [33-36.6]	15% [13.7-16.4]
	MPN	28.1% [24.6-31.7]	11.2% [8.8-13.8]	32.3% [28.3-36.4]	15.7% [12.7-19]
	Lymphoma	33.8% [28.5-39.2]	14.6% [10.9-18.9]	27.8% [22.6-33.3]	13.1% [9.3-17.4]
	OMHD	24.4% [17.6-31.8]	9.4% [5.3-15]	28.4% [20.8-36.4]	15% [9.4-21.9]
	Solid tumor	27.3% [23.6-31.2]	8.9% [6.6-11.5]	33% [28.8-37.3]	15.9% [12.7-19.4]
	BMFS	46.8% [28.6-63.1]	28.1% [13.8-44.3]	19.4% [7.6-35.2]	6.5% [1.1-19]
	P value	.030699	.0040158	.06477	.64736
IF MDS or MPN	MDS (n = 3258)	27.5% [25.9-29.1]	12.2% [11-13.4]	35% [33.2-36.9]	15.1% [13.8-16.5]
	MPN n = (663)	28.1% [24.6-31.7]	11.2% [8.8-13.8]	32.3% [28.3-36.4]	15.7% [12.7-19]
	P value	.76966	.48512	.17495	.67761
If solid tumor	Other solid tumor (n = 213)	22.6% [17.2-28.5]	8.2% [5-12.4]	34.4% [27.6-41.4]	13.8% [9.2-19.3]
	Breast cancer (n = 324)	30.5% [25.4-35.6]	9.3% [6.4-12.9]	32.1% [26.7-37.5]	17.2% [13.1-21.9]
	P value	.034002	.66059	.6327	.22558
Status at transplant	CR1	26.1% [24.4-27.8]	9.5% [8.4-10.7]	37% [35-39.1]	15.8% [14.2-17.4]
	CR2/3	29% [23.7-34.5]	11.8% [8.3-15.9]	33.3% [27.3-39.4]	17.8% [13.2-23.1]
	Active disease	30.4% [28.4-32.5]	14.9% [13.4-16.5]	29% [26.8-31.1]	13.6% [12-15.3]
	P value	.0048968	1.5171e-07	4.0372e-07	.027861
Donor type	MSD	25.5% [23.3-27.8]	11.2% [9.6-12.9]	34.8% [32.2-37.4]	17.1% [15.1-19.3]
	UD 10/10	28.2% [25.8-30.7]	11.3% [9.7-13.2]	35% [32.2-37.8]	15.3% [13.2-17.5]
	UD 9/10	34.1% [29.3-39]	15% [11.6-18.9]	33.6% [28.5-38.8]	16.2% [12.4-20.5]
	Haploidentical	24.7% [19.9-29.7]	9.5% [6.5-13.2]	24.3% [19.2-29.8]	9.1% [5.9-13]
	CBT	33.3% [26.2-40.6]	16.1% [10.9-22.1]	24% [17.6-31]	10.3% [6.2-15.7]
	P value	.0050115	.14505	.00022358	.0002393

Values are HRs with 95% CIs in brackets.

of relapse to be similar to previous studies and similarly was the major cause of treatment failure in our cohort [26-30]. Patients who received MAC as part of their treatment did have a significantly decreased risk of relapse, although no impact on survival was seen. Our study suggests that for patients who are deemed particularly high risk for relapse, it may be reasonable to consider MAC for suitable patients, although additional studies are needed to confirm this. Additionally, sAML patients with 1 or more variables that were associated with inferior survival outcomes such as active disease, adverse risk cytogenetics, and older age should be educated on these risks associated with sAML and transplantation. It may be that patients who harbor these higher risk factors should be considered for less intensive therapy other than HCT.

Some limitations of this study include its retrospective nature and its inherent drawbacks. Additionally, the categorization of MDS/MPN into 1 disease entity may perhaps be

Table 8
Multivariable Analysis of aGVHD and cGVHD

	GRFS			aGVHD Grades II-IV			cGVHD		
	HR	CI	*P*	HR	CI	*P*	HR	CI	*P*
CR1 (reference	1			1			1		
CR2/3	1.218	1.03-1.44	.02148	1.185	.907-1.548	.21445	1.146	.892-1.473	.28526
Active disease	1.546	1.425-1.676	<.001	1.309	1.149-1.491	.001	1.197	1.054-1.36	.00565
MDS (reference)	1			1			1		
MPN	1.21	1.069-1.369	.00258	1.089	.887-1.338	.41601	.928	.753-1.145	.48645
Lymphoma	1.273	1.062-1.526	.00891	1.365	1.032-1.804	.02916	.861	.634-1.17	.33986
OMHD	1.002	.768-1.306	.98944	.802	.512-1.258	.33677	.775	.505-1.189	.24358
Solid tumor	1.006	.878-1.154	.92844	1.048	.839-1.309	.67761	1.059	.862-1.301	.58461
BMFS	.5	.258-.969	.04007	1.733	.853-3.522	.12862	.436	.162-1.174	.10046
Age (per 10 yr)	1.058	1.02-1.098	.00261	.971	.917-1.028	.31767	1.014	.958-1.073	.63252
Good risk cytogenetics	1			1			1		
Intermediate risk	1.122	.801-1.572	.50255	.953	.578-1.572	.85122	1.485	.935-2.357	.09354
Adverse risk	1.682	1.196-2.367	.00283	1.062	.637-1.77	.81817	1.266	.783-2.048	.33535
NA/failed	1.328	.946-1.864	.10063	.968	.585-1.602	.89846	1.542	.966-2.459	.06923
KPS > 80%	.702	.618-.798	<.001	1.121	.889-1.412	.3348	1.084	.842-1.396	.53188
MSD	1			1			1		
UD 10/10	.918	.824-1.024	.12405	1.465	1.226-1.751	3e-05	1.084	.921-1.275	.33372
UD 9/10	1.111	.958-1.288	.1626	1.885	1.496-2.377	<10-5	1.188	.941-1.499	.14712
Haploidentical	1.037	.88-1.221	.66706	1.022	.768-1.361	.88051	.755	.568-1.005	.05406
CBT	1.044	.825-1.322	.71901	1.494	1.033-2.162	.03289	.434	.272-.69	.00043
Patient female vs. male	.925	.854-1.002	.05503	.864	.759-.983	.02672	.914	.806-1.036	.15804
Donor female vs. male	1.118	1.032-1.211	.00637	1.129	.992-1.285	.06676	1.269	1.122-1.435	.00014
MAC vs. RIC	1.05	.966-1.142	.25239	1.234	1.08-1.41	.00194	1	.876-1.141	.99958
Patient CMV positive	1.097	1.007-1.194	.03375	1.054	.918-1.209	.45777	1.001	.879-1.14	.99069
Donor CMV positive	.974	.898-1.056	.5222	.928	.814-1.058	.26465	1.055	.93-1.197	.40696
In vivo TCD	.885	.81-.968	.00718	.712	.618-.821	<.001	.634	.553-.726	<.001
Ex vivo TCD	1.235	.993-1.536	.05795	1.014	.687-1.498	.94245	.789	.515-1.208	.27592

oversimplifying the true biology of these diseases. Some data suggest that non-MDS–related sAML may have worse outcomes [12], and perhaps differentiating between these may be important in future studies because these may be more biologically distinct that previously believed. It is possible that patients in this cohort who had chronic myelomonocytic leukemia or other MPNs may have had poorer outcomes, but this was not able to be delineated within this study. However, consistent with the literature is that age, adverse cytogenetics, and poor disease control affect transplant outcomes, and it is possible these are more important variables than already known pretransplant patient variables. This may be helpful in patient counseling and guidance as to the expected outcomes post-transplant. Additionally, as data regarding molecular mutations such as *TP53*, *TET2, ASXL1*, *RUX1*, *NRAS*, and *IDH2* and their impact on AML outcomes, including in the post-transplant setting, continue to emerge, these also will need to be taken into consideration in future studies and risk stratification for patients undergoing HCT [31-33].

Small retrospective studies have shown comparable outcomes after allogeneic HCT for both patients with de novo and sAML in CR1 [34]. Although this study showed good 2-year OS for all patients in this cohort, future comparison studies with patients with de novo AML would be helpful to further prognosticate expected outcomes between these 2 groups of AML. Additionally, as more and more patients in need of transplant are undergoing haploidentical transplantation, particularly for those in need of urgent transplant without a matched sibling donor, this needs to be studied further for patients with this disease [35].

Finally, future data points and data analysis of patients with non–de novo AML may need to be distinguishable between the specific hematologic diseases associated with the diagnosis of AML. The World Health Organization criteria have evolved over the years, and the most recent 2016 version clearly distinguishes AML with MDS-related changes and therapy-related myeloid neoplasms as distinct subtypes [36]. Data collection of patients' disease characteristics both pre- and post-transplant is critical to reflect evolving disease categorization and subtypes as our understanding of the heterogeneity of these diseases evolves.

In summary, our study showed that patients with sAML had good 2-year OS, with nearly 45% OS after allogeneic HCT. However, patients who underwent RIC had higher incidence of relapses compared with those undergoing MAC. Additional patient variables that impacted outcomes included gender, active disease before transplant, adverse risk cytogenetics, older age, poor KPS, and CMV positivity. As such, all these variables need to be taken into consideration in patients with sAML who are in need of allogeneic HCT. Further prospective study is needed to determine if MAC is preferred in this disease for eligible patients. Further studies on the role of haploidentical transplant are also needed because this type of transplant is increasingly being used as a transplant option for patients in need of HCT. Finally, optimization of disease control pretransplant and post-transplant pre-emptive therapy to reduce risk of relapse may further improve outcomes in this high-risk patient population.

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