Evaluation of Trends and Prognosis Over Time in Patients with AML Relapsing After Allogeneic Hematopoietic Cell Transplant Reveals Improved Survival for Young Patients in Recent Years

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ABSTRACT

Purpose: Relapsed acute myeloid leukemia (AML) post allogeneic hematopoietic cell transplantation (allo-HCT) has a dismal prognosis.

Experimental Design: To assess prognosis of patients with recurrent AML post allo-HCT over time, we analyzed European Society for Blood and Marrow Transplantation registry data of 8,162 adult patients with AML who relapsed between 2000 and 2018 after allo-HCT performed in first complete remission from matched sibling, unrelated, or haploidentical donors.

Results: The 2-year overall survival (OS) rate from relapse was 17%. For 3,630 patients, <50 years of age, the 2-year OS continuously increased from 16% between 2000 and 2004 to 18% for 2005–2009, to 21% for 2010–2014, and to 26% for 2015–2018 ($P = 0.001$). Improvement over time was noted both after relapse within and beyond 6 months from allo-HCT. On multivariate analysis among patients <50 years of age, OS was positively affected by a later year of relapse (baseline: 2000–2004; HR, 0.82; $P < 0.02$ for 2010–2014 and HR, 0.72; $P = 0.0002$ for 2015–2018), good performance status, favorable cytogenetics, and longer time from transplant to relapse, but negatively affected by increasing age. In contrast, among 4,532 patients, >50 years of age, the year of relapse had no influence on OS (16% for 2000–2004 and 14% for 2015–2018; $P = 0.56$). Regarding treatment, encouraging results were observed after second allo-HCT, which was performed within 2 years after relapse in 17% of the entire cohort, resulting in a 2-year OS of 30.7%.

Conclusions: Outcome after posttransplant relapse among younger patients has improved significantly in recent years, likely reflecting, among other factors, the efficacy of posttransplant salvage including second allo-HCT.

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment modality for patients with acute myeloid leukemia (AML), particularly for those in first complete remission (CR1) who belong to the European LeukemiaNet intermediate- or high-risk prognostic groups, those who remain minimal residual disease (MRD) positive after induction therapy, as well as those beyond CR1. With recently decreasing nonrelapse mortality (NRM) rates, disease relapse is the main cause of failure of allo-HCT, occurring in 30%–40% of patients who underwent transplant (1). Treatment options for posttransplant relapse traditionally include reduction/withdrawal of immunosuppression, conventional chemotherapy, donor lymphocyte infusion (DLI), and second allo-HCT, either alone or in sequence/combination (2). Unfortunately, no standard treatment has been established so far in this challenging clinical situation, and in earlier studies, long-term overall survival (OS) was constantly below 20% (3–9). Some studies have reported improved outcomes after

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Translational Relevance

In this large registry analysis of 8,162 patients with acute myeloid leukemia with relapse after transplantation, we show a steady increase in 2-year survival from relapse for younger patients over time, reflecting the efficacy of posttransplant salvage, including second transplant. This improvement over time was noted in intermediate cytogenetic risk group, and in either *FLT3* wild-type or *FLT3* internal tandem duplication. Importantly, improvement over time was noted both in early (<6 months) and late (>6 months) relapse. Finally, more than 30% 2-year survival was observed among patients who could receive a second allogeneic stem cell transplantation.

intensive therapy (6, 10, 11). Nevertheless, survival was dismal for patients who had early relapse after transplant (12–14) and these patients are frequently offered palliative care only.

Recent years have witnessed significant changes in the characteristics of patients undergoing allo-HCT and the conditioning regimen. Furthermore, new strategies for the management of posttransplant AML relapse have become available (15–17), including the use of hypomethylating agents and targeted therapies, such as tyrosine kinase inhibitors (sorafenib and midostaurin), notably in patients with *FLT3* mutations. Furthermore, increased availability of alternative donors (either well-matched unrelated or haploidentical family donors) facilitate second allo-HCT as salvage therapy. The aim of this study was to evaluate whether the entirety of these recent developments has influenced patients characteristics, risk factors, and outcome of AML relapse after allo-HCT over time. We used a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

Materials and Methods

Study design and data collection

This was a retrospective, registry-based, multicenter analysis. Data were provided and approved by the Acute Leukemia Working Party of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centers, which are required to report all consecutive HCTs and follow-ups once a year. Audits are routinely performed to determine the accuracy of the data. Since January 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT, following the guidelines of the Declaration of Helsinki, 1975. Eligibility criteria for this analysis included age ≥18 years, first allo-HCT for AML in CR1, and documented hematologic relapse after allo-HCT between 2000 and 2018. Patients only showing decreasing donor chimerism or cytogenetic/molecular relapse were excluded. Donor types included matched sibling donors (MSDs), unrelated donors (UDs) regardless of HLA mismatch, and haploidentical donors. Cord blood transplants were excluded because of the missing opportunity of DLI and second allo-HCT from the same donor for management of relapse. The stem cell source was bone marrow (BM) or G-CSF–mobilized peripheral blood (PB). Patients who received *in vitro* T-cell depletion were excluded.

Variables collected included recipient age at transplant and at relapse, recipient and donor gender, date of diagnosis, karyotype and molecular profile at diagnosis, *de novo* versus secondary AML, year of transplant, year of relapse, time from transplant to relapse, Karnofsky performance status (KPS) score at time of transplant, and transplant-related factors including conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, donor type, stem cell source (BM or PB), patient and donor cytomegalovirus (CMV) status, and finally the development of acute and chronic GVHD before relapse. Relapse-associated variables included the interval from allo-HCT to relapse, OS from relapse, and cause of death. For recipients of a second allo-HCT, time from relapse to second transplant, conditioning intensity, donor type, and relapse after second allo-HCT were recorded.

Definitions

Myeloablative conditioning (MAC) was defined as a regimen containing either total body irradiation with a dose greater than 6 Gy, a total dose of oral busulfan greater than 8 mg/kg, or a total dose of intravenous busulfan greater than 6.4 mg/kg. All other regimens were defined as reduced-intensity conditioning (RIC; ref. 18). The diagnosis and grading of acute (19) and chronic GVHD (20) were performed by transplant centers using standard criteria. Hematologic relapse was defined by recurrence of blasts in the PB or infiltration of the BM by ≥5% blasts. Early relapse was defined as relapse within 6 months from allo-HCT. Second allo-HCT was defined as infusion of donor PB or BM stem cells, following MAC or RIC, with immunosuppression for GVHD prevention. Cytogenetic subgroups were classified according to the Medical Research Council (MRC) classification (21).

Statistical analysis

Endpoints included 2-year OS from relapse, causes of death, the incidence of second allo-HCT, and OS after second allo-HCT. OS was defined time from date of relapse or date of second allo-HCT to death from any cause. Surviving patients were censored at the time of last contact. All outcomes were censored at 2 years after relapse. The probability of OS was calculated using the Kaplan–Meier method. For univariate analyses, factors known from the literature to possibly influence outcome were included; continuous variables were categorized and the median was used as a cut-off point. Univariate comparisons for OS were performed using the log-rank test. Cumulative incidence was used to estimate the incidence of salvage second HCT, death being a competing event. A Cox proportional hazards model was used for multivariate regression, all the variables significant at 0.05 in the univariate analysis were included, and backward stepwise elimination was applied to select variables for the final model. Multivariate results are expressed as an HR with a 95% confidence interval (CI). All tests were two-sided. The type 1 error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. All analyses were performed using SPSS 24.0 (SPSS Inc.) and R version 3.4.0 (R Core Team. R: a language for statistical computing. 2014. R Foundation for Statistical Computing).

Results

Patient and transplant characteristics

Overall, 8,162 adult patients with AML who relapsed between 2000 and 2018 after allo-HCT in CR1 were included (**Table 1**). Median age at relapse was 52 years (range, 18–80), with a continuous increase from 44 years among 692 patients relapsing between 2000 and 2004 to 56 years among 2,878 patients relapsing between 2015 and 2018 ($P < 0.001$). Median time from transplant to relapse was 6 months (range, 0.1–295 months) with no change over time. Overall, 18% of patients had a secondary AML, with a significant increase over time ($P < 0.001$). Cytogenetic data at diagnosis were available for 56% of patients, 218 (3%), 2,910 (36%), and 1,437 (18%) patients had a good, intermediate, and poor karyotype, respectively, with a slight increase of unfavorable

cytogenetics over time. Information on *FLT3* and *NPM*1 mutation status was available for 2,737 (34%) and 2,499 (31%) patients, respectively, with a continuously increasing percentage in recent years. Most relapsing patients had received RIC (51%) and peripheral blood stem cell grafts (84%), with a significant increase for both modalities over time ($P < 0.001$) (**Table 2**). Acute GVHD grade II–IV and chronic GVHD had occurred before relapse in 21% and 21% of patients, respectively.

OS and cause of death

Median follow-up for surviving patients was 35 months. For the entire cohort, the 2-year OS after relapse was 17% (95% CI, 17–18%). Original disease was the cause of death in 77% of deceased patients, followed by infections (11%) and GVHD (5%). In univariate analysis, the 2-year OS after relapse increased from 16% for patients relapsing between 2000 and 2004 to 16.6% for the period 2005–2009, to 17.3% for 2010–2014, and to 18.2% for 2015–2018 ($P = 0.002$). Time from transplant to relapse significantly affected 2-year OS after relapse, which varied from 10% for patients relapsing within 6 months after allo-HCT to 24.3% for patients relapsing after 6 months ($P = 0.001$). Finally, patients with very late relapse (more than 2 years after allo-HCT) had a 2-year OS after relapse of 37.9%. In multivariate analysis, an interaction between year of transplant and patient age was noted. Therefore, a separate analysis was performed for patients aged up to and beyond 50 years at relapse.

Survival from relapse in younger patients

For 3,630 patients aged ≤50 years at relapse, patient and transplant characteristics are summarized in Supplementary Tables S1 and S2. Median age at relapse continuously increased over time from 35.7 years for patients relapsing between 2000 and 2004, to 39.4 years for 1,007 patients who relapsed between 2015 and 2018 ($P < 0.001$). Matched siblings represented the most frequently used donor type, however, showing a sharp and progressive decrease over time of this donor source, from 72% for patients relapsing during the period of 2000–2004 to 39% for the period 2015–2018, accompanied by increased UD and haploidentical donors over time ($P < 0.001$). A slight increase of patients with unfavorable cytogenetics was observed over time. Most relapsing patients had received MAC and PB as the stem cell source, with trends over time showing increased use of RIC, PB, and *in vivo* T-cell depletion. While no significant change in acute GVHD grade II–IV before relapse was noted, chronic GVHD before relapse occurred in 27% of patients relapsing in 2000–2004, 20% for 2005–2009, 22% for 2010–2014, and 17% for 2015–2018, respectively ($P < 0.001$).

Among these younger patients, the 2-year OS after relapse increased from 16% for patients relapsing between 2000 and 2004 to 18% for the period 2005–2009, 21% for 2010–2014, and 26% for 2015–2018 ($P = 0.001$; **Fig. 1A** and **C**). Interestingly, a change over time was noted in the cause of death, original disease accounted for 81% of death cases, followed by infections (8%) and GVHD (4%) for patients relapsing between 2000 and 2004, whereas original disease accounted for 63% of death cases, followed by infections (18%) and GVHD (7%) for patients relapsing in 2015–2018.

As in the entire cohort, time from transplant to relapse significantly affected survival after relapse in this subgroup, with 2-year OS after relapse of 13% and 27% for patients relapsing within and beyond 6 months after allo-HCT, respectively ($P = 0.001$). Importantly, improved survival over time was noted for both early and late relapse, with 2-year OS increasing from 10% to 17% among patients relapsing within 6 months from allo-HCT ($P = 0.001$), and increasing from 20.5% to 33% among patients relapsing beyond 6 months ($P = 0.001$; Supplementary Table S3). Finally, patients with very late relapse (more than 2 years after allo-HCT) had a 2-year OS after relapse of 45%.

Table 1. Patients baseline characteristics.

	2000–2004 *n* (%)	2005–2009 *n* (%)	2010–2014 *n* (%)	2015–2018 *n* (%)	*P*	Entire population *n* (%)
Total number of patients	692 (100)	1,734 (100)	2,858 (100)	2,878 (100)		8,162 (100)
Patient gender (missing)	(0)	(1)	(3)	(3)		(7)
Male	388 (56)	914 (53)	1,510 (53)	1,529 (53)	0.47	4,341 (53)
Female	304 (44)	819 (47)	1,345 (47)	1,346 (47)		3,814 (47)
Patient age at HCT1 median (range)	42 (18–76)	48 (18–75)	52 (18–80)	55 (18–78)	<10–3	51 (18–80)
Patient age at relapse median (range)	44 (18–77)	49 (18–75)	53 (18–80)	56 (18–78)	<10–3	52 (18–80)
Year of relapse median	2003	2007	2012	2016		2013
Type of AML						
De novo	604 (87)	1,451 (84)	2,318 (81)	2,332 (81)	<0.001	6,705 (82)
Secondary	88 (13)	283 (16)	540 (19)	546 (19)		1457 (18)
Cytogenetics molecular risk score (NA/failed)	[273 (39)]	[791 (46)]	[1,567 (55)]	[966 (34)]		[3,597 (44)]
Good	27 (4)	48 (3)	70 (2)	73 (3)	<0.001	218 (3)
Intermediate	279 (40)	637 (37)	810 (28)	1,184 (41)		2,910 (36)
Poor	113 (16)	258 (15)	411 (14)	655 (23)		1,437 (18)
FLT3 status (missing)	(510)	(1,257)	(2,133)	(1,525)		(5,425)
FLT3 neg	159 (87)	350 (73)	467 (64)	889 (66)	<0.001	1,865 (68)
FLT3 pos	23 (13)	127 (27)	258 (36)	464 (34)		872 (32)
NPM1 status (missing)	(534)	(1,355)	(2,205)	(1,569)		(5,663)
NPM1 neg	155 (98)	331 (87)	513 (79)	929 (71)	<0.001	1,928 (77)
NPM1 pos	3 (2)	48 (13)	140 (21)	380 (29)		571 (23)
Patient CMV serology (missing)	(202)	(352)	(102)	(61)		(717)
CMV neg	171 (35)	492 (36)	898 (33)	870 (31)	0.014	2,431 (33)
CMV pos	319 (65)	890 (64)	1,858 (67)	1,947 (69)		5,014 (67)

Abbreviations: HCT1, first hematologic stem cell transplant; NA, not applicable; neg, negative; pos, positive.

Table 2. Donor and first transplant characteristics.

	2000–2004 *n* (%)	2005–2009 *n* (%)	2010–2014 *n* (%)	2015–2018 *n* (%)	*P*	Entire population *n* (%)
Total numbers of patients	692 (100)	1,734 (100)	2,858 (100)	2,878 (100)		8,162 (100)
Donor gender (missing)	(18)	(19)	(34)	(30)		(101)
Male	428 (64)	1,034 (60)	1,780 (63)	1,908 (67)	<0.001	5,150 (64)
Female	246 (37)	681 (40)	1,044 (37)	940 (33)		2,911 (36)
Donor CMV serology	(217)	(358)	(106)	(77)		(758)
CMV neg.	213 (45)	645 (47)	1,297 (47)	1,288 (46)	0.72	3,443 (47)
CMV pos	262 (55)	731 (53)	1,455 (53)	1,513 (54)		3,961 (53)
Donor type						
MSD	500 (72)	1,095 (63)	1,367 (48)	1,021 (35)	<0.001	3,983 (49)
UD	181 (26)	608 (35)	1,384 (48)	1,650 (57)		3,823 (47)
Haplo	11 (2)	31 (1.8)	107 (4)	207 (7)		356 (4)
Median months HCT1 relapse (range)	6 (0.1–121)	6 (0.3–279)	6 (0.1–242)	6.4 (0.1–295)	0.027	6 (0.1–295)
Year of HCT1 median (range)	2002 (1991–2004)	2006 (1986–2009)	2011 (1992–2014)	2015 (1992–2018)	<10−3	2011 (1986–2018)
Female → male transplant (missing)	(9)	(11)	(23)	(21)		(64)
No female → male	560 (82)	1,410 (82)	2,352 (83)	2,462 (86)	<0.001	6,784 (84)
Female → male	123 (18)	313 (18)	483 (17)	395 (14)		1,314 (16)
Stem cell source						
BM	222 (32)	340 (20)	447 (16)	329 (11)	<0.001	1,338 (16)
PB	470 (68)	1,394 (80)	2,411 (84)	2,549 (89)		6,824 (84)
Conditioning intensity						
MAC	458 (66)	933 (54)	1,346 (47)	1,233 (43)	<0.001	3,970 (49)
RIC	234 (34)	801 (46)	1,512 (53)	1,645 (57)		4,192 (51)
In vivo TCD (missing)	(145)	(313)	(61)	(29)		(548)
No *in vivo* TCD	364 (67)	768 (54)	1,235 (44)	1,050 (37)	<0.001	3,417 (45)
In vivo TCD	183 (33)	653 (46)	1,562 (56)	1,799 (63)		4,197 (55)
PTCY (missing)	(156)	(331)	(82)	(55)		(624)
No PTCY	534 (100)	1,403 (100)	2,702 (97)	2,529 (90)	<0.001	7,168 (95)
PTCY	2 (0.4)	0 (0)	74 (3)	294 (10)		370 (5)
Median follow-up months (IQR)	159 (86–184)	110 (69–133)	58 (36–78)	18.5 (10–32)		46 (18–89)
aGVHD II before relapse	136 (21)	353 (21)	573 (21)	565 (21)	0.97	1,627 (21)
cGVHD before relapse	148 (25)	324 (21)	560 (22)	521 (19)	0.017	1,553 (21)

Abbreviations: aGVHD: acute GVHD; cGVHD, chronic GVHD; haplo, haploidentical donor; PTCY, posttransplant cyclophosphamide; TCD, T-cell depletion.

On multivariate analysis (**Table 3**), OS from relapse was positively affected by the year of relapse after 2009 compared with the period 2000–2004 (HR, 0.82; $P < 0.02$ for patients relapsing from 2010 to 2014 and HR, 0.72; $P = 0.0002$ for patients relapsing from 2015 to 2018), and a good KPS score at transplant and a longer time from transplant to relapse also improved OS. Increasing patient age and intermediate or poor cytogenetic risk group negatively affected OS. Other patient, donor, and transplant characteristics, including conditioning intensity, had no significant effect on OS in younger patients.

When different cytogenetic risk groups were analyzed, improved survival over time was noted in patients with intermediate-risk karyotype with 2-year OS after relapse increasing from 17% for 486 patients relapsing between 2000 and 2009 to 27% for 767 patients relapsing between 2010 and 2018 ($P = 0.001$), whereas no significant change was noted for patients with favorable (38% vs. 40%; $P = 0.47$) and adverse cytogenetics (15% and 14%; $P = 0.22$). Importantly, improved survival over time was noted for both patients with *FLT3* wild-type or internal tandem duplication (ITD; Supplementary Table S4).

Survival from relapse for older patients

Patient and transplant characteristics of 4,532 patients aged >50 years at relapse are summarized in Supplementary Tables S5 and S6. Median age at relapse continuously increased over time from 56.2 years for patients who relapsed between 2000 and 2004, to 61.4 years for 1,871 patients who relapsed between 2015 and 2018 ($P < 0.001$). Before 2009, most relapsing patients had an MSD with, however, a sharp and progressive decrease over time of this donor source, from 72% for patients relapsing in 2000–2004 to 33% for 2015–2018, accompanied with increased UD, which became the main source of stem cells in 2010–2014 (53%) and 2015–2018 (59%), as well as increased use of haploidentical donors over time ($P < 0.001$). Most relapsing patients had received RIC with no significant change over time. An increased use of PB ($P < 0.001$) and *in vivo* T-cell depletion ($P < 0.001$) over time was observed. No significant change in acute GVHD grade II–IV or chronic GVHD before relapse was noted.

For these older patients, the 2-year OS from relapse was not affected by the year of relapse (16% for 2000–2004; 15% for 2005–2009 and for 2010–2014, and 14% for 2015–2018; $P = 0.56$; **Fig. 1B** and **C**). Time from transplant to relapse significantly affected survival after relapse, with 2-year OS after relapse of 7.6% for patients relapsing within 6 months after allo-HCT compared with 21.6% for patients relapsing after 6 months ($P = 0.001$). Finally, patients with very late relapse (more than 2 years after allo-HCT) had a 2-year OS after relapse of 33%.

On multivariate analysis (**Table 3**), as in the younger group, OS from relapse was negatively affected by a shorter time from transplant to relapse, reduced KPS score, increasing patient age, and unfavorable cytogenetics. In addition, OS from relapse was superior in patients initially transplanted from an MSD and using RIC regimen. Other

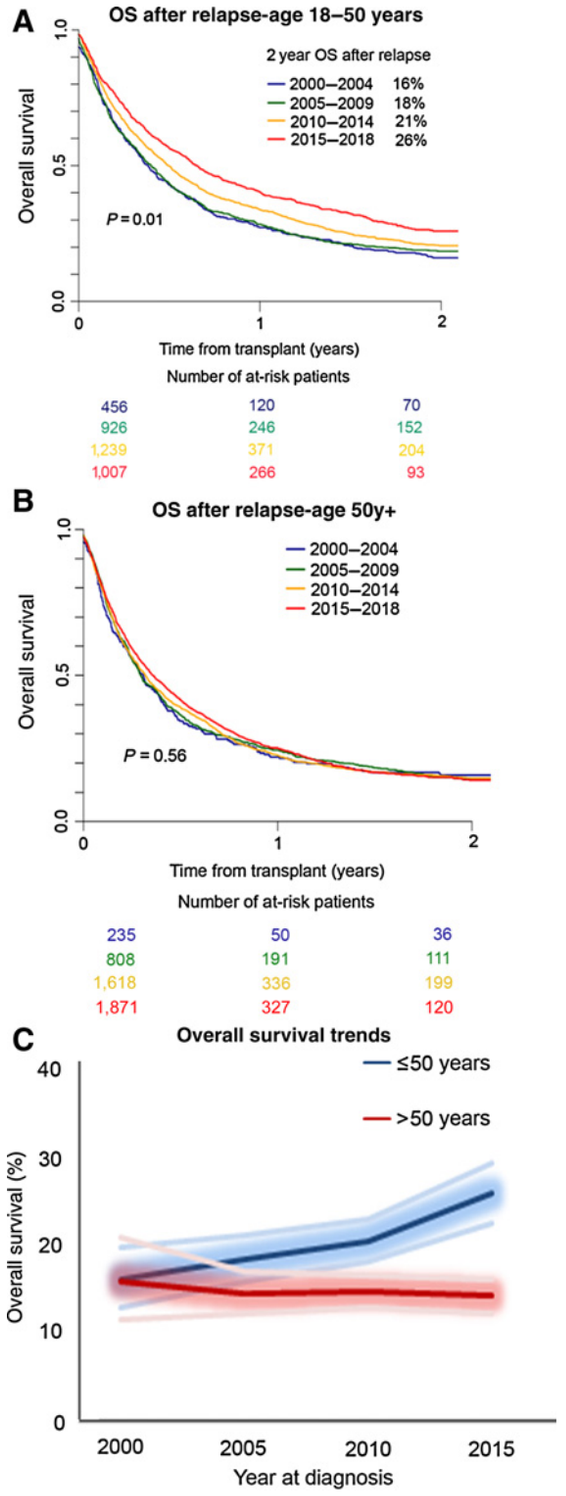

Figure 1.

A, OS from relapse over time for patients less than or equal to 50 years of age according to treatment period. **B,** OS from relapse over time for patients older than 50 years of age according to treatment period. **C,** Graphical representation of trends in 2-year OS from relapse over time for younger (≤50 years old) and elderly (>50 years old) patients.

Table 3. Multivariate analysis for OS at 2 years after relapse for patients ≤50 years at relapse (n = 3,630).

	HR (95% CI) *P*
Year of relapse	
2000–2004 (reference)	1
2005–2009	1.01 (0.85–1.19) 0.95
2010–2014	0.82 (0.69–0.96) 0.017
2015–2018	0.72 (0.6–0.85) 0.0002
Patient age at HCT (per 10 y)	1.1 (1.05–1.16) 0.0001
Secondary AML	1.07 (0.93–1.23) 0.35
Cytogenetics (MRC)	
Good (reference)	1
Intermediate	1.51 (1.18–1.94) 0.001
Poor	1.9 (1.47–2.46) <10–5
NA/failed	1.77 (1.38–2.27) <10–5
KPS ≥ 80 at HCT	0.74 (0.58–0.93) 0.01
Donor	
MSD (reference)	1
UD	0.99 (0.9–1.09) 0.90
Other relative	0.94 (0.73–1.19) 0.59
PB vs. BM	1.08 (0.97–1.21) 0.18
Female to male	1.1 (0.98–1.24) 0.12
Pat. CMV positive	1.05 (0.95–1.16) 0.38
Donor CMV positive	0.98 (0.88–1.08) 0.62
Time HCT1-relapse (mo)	0.97 (0.97–0.98) <10–5
RIC vs. MAC HCT1	0.91 (0.82–1.01) 0.087

Abbreviations: mo, months; NA: not applicable, pat., patient.

patient, donor, and transplant characteristics, including the year of relapse, had no significant effect on OS in older patients.

Second transplant

A second allo-HCT was performed within 2 years after relapse in 1,407 (17%) patients after a median of 107 days from relapse [interquartile range (IQR), 62–189; **Table 4**]. The same donor as for HCT1 was used in 330 patients (30%) and RIC was utilized in 1,055 (77%) patients. Trends over time showed an increase in the time from relapse to second allo-HCT from 79 days for patients relapsing in 2000–2004 to 87, 121, and 118 days for 2005–2009, 2010–2014, and 2015–2018, respectively ($P < 0.001$), as well as a sharp increase in the use of a different donor from 31% in 2000–2004 to 53%, 77%, and 80% for 2005–2009, 2010–2014, and 2015–2018, respectively ($P = 0.001$; **Table 4**). Overall, second allo-HCT resulted in an encouraging 2-year OS from date of transplant of 30.7% (95% CI, 28–33.4%),

Table 4. Multivariate analysis for OS at 2 years after relapse for patients >50 years ($n = 4,532$).

	HR (95% CI) *P*
Year of relapse	
2000–2004 (reference)	1
2005–2009	1.1 (0.9–1.35) 0.33
2010–2014	1.1 (0.91–1.33) 0.35
2015–2018	1 (0.82–1.21) 0.98
Patient age at HCT (per 10 y)	1.1 (1.04–1.17) 0.002
Secondary AML	0.92 (0.85–1) 0.057
Cytogenetics (MRC)	
Good (reference)	1
Intermediate	1.27 (0.93–1.74) 0.13
Poor	1.56 (1.14–2.15) 0.006
NA/failed	1.36 (1–1.86) 0.054
KPS ≥ 80 at Tx	0.69 (0.58–0.82) <10–4
Donor	
MSD (reference)	1
UD	1.1 (1.02–1.19) 0.02
Other relative	1.21 (1.01–1.46) 0.04
PB vs. BM	1.03 (0.92–1.16) 0.59
Female to male	0.96 (0.87–1.06) 0.46
Pat. CMV positive	1.07 (0.98–1.16) 0.12
Donor CMV positive	1 (0.93–1.08) 0.96
Time HCT1-relapse (mo)	0.98 (0.98–0.98) <10–5

Abbreviations: mo: months; pat., patient.

interestingly without differences between age groups (30.5% for younger patients vs. 30.9% for older patients; $P = 0.3$; **Fig. 2A**).

For patients ≤50 years at relapse, the incidence of second allo-HCT was 23%, 21%, 22%, and 28% for 2000–2004, 2005–2009, 2010–2014, and 2015–2018, respectively ($P = 0.003$). Trends over time showed a progressive increase in 2-year OS from second transplant from 22.6% for 2000–2004, to 28.3% for 2005–2009, 32.5% for 2010–2014, and 32.3% for 2015–2018, respectively ($P = 0.01$; **Fig. 2B**). Conversely, for older patients at relapse (>50 years), the incidence of second allo-HCT decreased from 18% for the period 2000–2004, to 15% in 2005–2009, 11% in 2010–2014, and 11% in 2015–2018 ($P < 0.001$). No significant change in 2-year OS from second transplant was noted over time for these older patients.

Discussion

This retrospective analysis of a homogenous cohort of 8,162 patients with hematologic relapse after allo-HCT for AML in CR1 analyzed trends in patients' characteristics and outcome over the last two decades. Numbers of reported relapses increased over the years, reflecting the increasing numbers of allo-HCT in general, the increasing numbers of reporting centers, and most likely also the increasing use of RIC regimen over time. Overall, the 2-year OS from relapse was 17%, with the original disease being the primary cause of death. Over time, we observed a steady increase in 2-year survival from 16% to 26% ($P = 0.001$) among patients ≤50 years at relapse, particularly in patients with an intermediate cytogenetic risk, including *FLT3* wild-type and *FLT3*-ITD. Importantly, improvement over time was noted both in early (<6 months) and late (>6 months) relapse. In contrast, no better survival over the years was seen in older patients (**Fig. 1**).

The improvement among younger patients can be explained by multiple factors, which most likely all play a certain role. First, RIC was used more often in recent years. Hence, patients were less heavily pretreated and may have been able to tolerate more intensive treatments for relapse, including second allo-HCT. Furthermore, patients relapsing more recently had received more T-cell–depleted grafts and had developed less graft-versus-host disease (cGVHD) before relapse. Therefore, in these patients the graft-versus-leukemia effect may have been less exploited after the first allo-HCT (22), rendering the disease more sensitive to graft-versus-leukemia–based treatments for post-transplant relapse.

Second, the management of posttransplant relapse itself might have improved for several reasons, including increased availability of specific and tolerable antileukemic drugs, such as hypomethylating agents *or* FLT3 inhibitors, a better understanding of the genomic landscape of AML, and the more frequently performed molecular characterization of the leukemia (16, 23–26). Unfortunately, we did not have enough details on treatment modalities to prove this. However, the idea is supported by particular improvement among patients with intermediate cytogenetics, and by the fact, that AML bearing an *FLT3*-ITD mutation was the only genetically defined risk group with improved survival over time. In contrast, for example, AML with unfavorable cytogenetics, against which no targeted treatment has been discovered in recent years, did not show improved outcome. In addition, a diminishing frequency of leukemia-related death over the years suggests a better disease control, although at the possible expense of a relative increase in NRM.

Third, increasing understanding of the mechanisms of relapse (27) may have assisted in choosing optimal salvage strategies and avoiding approaches with obviously limited chance of success, such as applying DLI or a second allo-HCT from the same donor to a patient with loss of mismatched HLA. Finally, better patient selection, easier access to alternative donors, and better ways to initial disease control may have contributed to the increased rate of second allo-HCT in younger adults, rising from 23% to 28% ($P = 0.003$), with increasing use of a different donor over time and an encouraging 2-year OS beyond 30% in the years 2010–2015. Hence, although only a minority had received a second allo-HCT, this procedure seems to contribute to long-term remissions and improved outcome. However, a detailed analysis of second allo-HCT was not within the scope of this analysis.

In contrast, the lack of improvement in older patients may be due to increasing age, a more aggressive disease biology (represented among other factors by a higher percentage of secondary acute myeloid leukemia and slightly increasing number of unfavorable cytogenetics over time), and a generally lower feasibility of curative options including second allo-HCT. Molecular mutations such as *FLT3*-ITD, against which specific therapies have been developed, are less frequent among the elderlies, who, in contrast, have a higher risk to bear poor risk genetics (28). The percentage of elderly

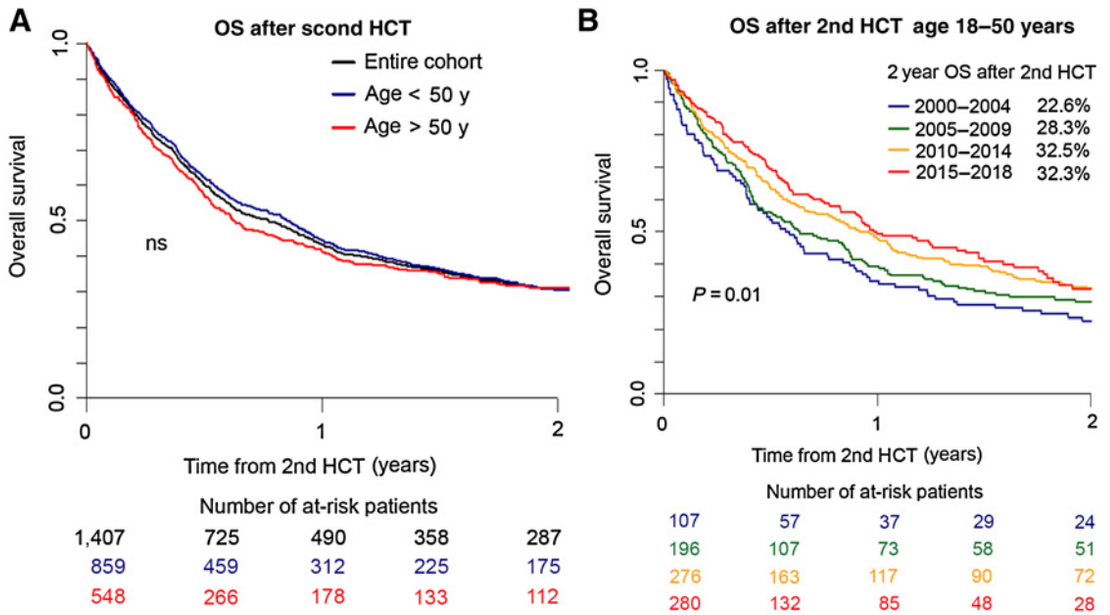

Figure 2.

A, OS after second HCT for all patients, patients less than or equal to 50 years, and patients older than 50 years. **B,** OS after second HCT over time for patients less than or equal to 50 years according to treatment period.

patients undergoing a second allo-SCT has decreased over time. However, in those elderly patients who finally received a second transplant, outcome was comparable with younger patients.

Besides the year of relapse, multivariate analysis confirmed known predictors of OS from posttransplant relapse as patient age, KPS score, remission duration post allo-HCT, and cytogenetic risk at initial diagnosis in both younger and older patients. A remission below 6 months has been by far the strongest negative prognostic factor in virtually all studies on AML relapse posttransplant (2–4, 10, 29). Best supportive care is a frequently recommended strategy for those patients. Against this background, improvement of OS over time even among patients with early-relapse posttransplant was a very encouraging finding in the group of younger patients. Although results are still unsatisfying, this observation can justify to thoroughly look for a suitable, individual treatment strategy in each patient.

Survival rates of >35% among patients relapsing >2 years after allo-HCT is another encouraging finding in both younger and elderly patients. Either these patients were able to tolerate more intensive treatments due to the longer interval from HCT, or less aggressive approaches, such as a combination of hypomethylating agents +/− DLI (15, 30), might have controlled the leukemia in these probably less proliferative diseases. However, we again could not support this suggestion by our data due to missing information on applied treatment.

Some limitations of our retrospective study must be considered. These include the lack of information on MRD prior to (first) allo-HCT, although this might not be of great relevance for this study including only patients with hematologic relapse posttransplant. Furthermore, we frequently missed information on molecular genetics other than *NPM1* and *FLT3*-ITD mutations. As discussed above, the lack of detailed information about the treatment of posttransplant relapse besides second allo-HCT in a considerable percentage of patients is another limitation. Similarly, we missed reliable data on maintenance therapy, once a second remission had been achieved. This unfortunately precluded to exactly define the role of different innovations for the observed improvement in outcome among younger patients, which, however, was not the main focus of this study, investigating overall trends in relapsed patients over time.

In summary, the study so far represents the largest analysis assessing trends over time and predictive factors for outcome for patients with relapsed AML after allo-HCT. It can serve as benchmark concerning outcome for future studies. Although comparison among different treatment strategies was not performed, improved overall outcome among younger patients in recent years, including those with early relapse, >35% long-term survivors among patients relapsing beyond 2 years from allo-HCT, and a 30% OS among both younger and elderly patients who could receive a second allo-HCT are encouraging findings. Nevertheless, there is still much room for improvement within the treatment of posttransplant relapse in AML, and further studies will have to define optimized and individualized strategies for each patient.

Disclosure of Potential Conflicts of Interest

A. Bazarbachi reports grants and personal fees from Novartis, Roche, Takeda, Jansen, Celgene, Pfizer, and Hikma, personal fees from Jazz, Sanofi, Amgen, and AstraZeneca, and grants from Astellas outside the submitted work. D. Beelen reports personal fees from Medac GmbH, Germany (consultancy, travel support) outside the submitted work. G. Socié reports other from Novartis (advisory board), Incyte (advisory board), ElsaLys (advisory board), and Therakos (speaker bureau) and grants from Alexion outside the submitted work. I. Abou Dalle reports personal fees from Novartis (honoraria) outside the submitted work. G. Bug reports personal fees from Jazz, Hexal, Pfizer, and Eurocept, grants and personal fees from Celgene (travel grant) and Gilead (travel grant), personal fees and other from Novartis (research fund), and grants from Sanofi (travel grant) and Neovii (travel grant) outside the submitted work. J. Esteve reports personal fees from Astellas, AbbVie, Jazz Pharmaceuticals, Novartis, Celgene, and Pfizer outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

A. Bazarbachi: Conceptualization, formal analysis, supervision, methodology, writing-original draft, project administration, writing-review and editing. **C. Schmid:** Conceptualization, formal analysis, methodology, writing-original draft, writing-review and editing. **M. Labopin:** Formal analysis, methodology, writing-review and editing. **D. Beelen:** Writing-review and editing, included patients. **I. Wolfgang Blau:** Writing-review and editing, included patients. **V. Potter:** Writing-review and editing, included patients. **R. Niittyvuopio:** Writing-review and editing, included patients. **G. Socié:** Writing-review and editing, included patients. **D. Blaise:** Writing-review and editing, included patients. **J. Sanz:** Writing-review and editing, included patients. **F. Ciceri:** Writing-review and editing, included patients. **I. Abou Dalle:** Writing-review and editing. **A. Spyridonidis:** Writing-review and editing, included patients. **G. Bug:** Writing-review and editing, included patients. **J. Esteve:** Writing-review and editing, included patients. **B.N. Savani:** Writing-review and editing. **A. Nagler:** Writing-review and editing. **M. Mohty:** Conceptualization, resources, formal analysis, supervision, project administration, writing-review and editing.

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