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Survival of AML patients relapsing after allogeneic hematopoietic cell transplantation: a CIBMTR study

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Abstract

Acute myeloid leukemia (AML) relapse after allogeneic hematopoietic cell transplantation (alloHCT) remains a major therapeutic challenge. We studied outcomes of 1788 AML patients relapsing after alloHCT (1990–2010) during first or second complete remission (CR) to identify factors associated with longer post-relapse survival. Median time of post HCT relapse was 7 months (mo; range, 1–177). At relapse, 1231 patients (69%) received intensive therapy, including chemotherapy (CT) alone (n=660), donor lymphocyte infusion (DLI)±CT (n=202; %), or 2nd alloHCT±CT ±DLI (n=369), with subsequent CR rates of 29%. Median follow-up after relapse was 39 mo (range, <1–193). Survival for all patients was 23% at 1 year post-relapse; however, 3-yr overall survival correlated with time from HCT to relapse (4% for relapse during 1–6 mo period, 12% during 6 mo-2 yr, 26% during 2–3 yr, and 38% for ≥3 yr). In multivariable analysis, lower mortality was significantly associated with longer time from alloHCT to relapse (RR 0.55 for 6 mo-2 yr, RR 0.39 for 2–3 yr, and RR 0.28 for ≥3 yr; p<0.0001) and a 1st HCT using reduced-

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intensity conditioning (RR=0.77; 95% CI 0.66–0.88, p=0.0002). In contrast, inferior survival was associated with age >40 yr (RR=1.42, 95% CI 1.24–1.64; p<0.0001), active GVHD at relapse (RR=1.25, 95% CI 1.13–1.39; p<0.0001), adverse cytogenetics (RR=1.37, 95% CI 1.09–1.71; p=0.0062), mismatched URD (RR=1.61, 95% CI 1.22–2.13; p=0.0008), and use of cord blood for 1st HCT (RR=1.23, 95% CI 1.06–1.42; p=0.0078). AML relapse after alloHCT predicted poor survival; however, patients who relapsed ≥6 mo after their initial alloHCT had better survival and may benefit from intensive therapy such as 2nd alloHCT±DLI.

Keywords

AML; relapse; allogeneic transplant; DLI; second transplant

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative treatment option for patients with acute myeloid leukemia (AML); however, relapse accounts for approximately 40% of alloHCT treatment failures. Among relapsed patients the 2-year postrelapse survival rate is reported at less than 20%. (1–7) Unfortunately, sustainable remissions are rare in patients with post-transplant AML relapse, especially for those relapsing soon after alloHCT. (8, 9) Commonly used treatment options for relapsed patients include intensive chemotherapy with or without donor lymphocyte infusion (DLI), second alloHCT, withdrawal of immunosuppression, or supportive care.(4, 7, 8, 10–13) Treatment decisions for management of relapsed AML could be improved by identifying prognostic factors associated with post-relapse survival and developing a risk stratification model.

A recent study by the European Blood and Marrow Transplantation (EBMT) group identified several prognostic factors associated with improved survival among AML patients who relapsed after reduced-intensity conditioning (RIC) alloHCT: longer interval from transplant to relapse, low bone marrow tumor burden at relapse, and absence of acute graft versus host disease (GVHD). Longer survival was seen primarily among patients who achieved complete remission (CR) with chemotherapy followed by either DLI or a second alloHCT.(1) These findings are consistent with other single-institution reports of alloHCT outcomes among patients treated for relapsed AML. These reports suggested that intensive therapy resulted in better survival than withdrawal of immunosuppression alone (5, 7, 11), independent of donor source or intensity of initial conditioning;(7) however, a detailed analysis of prognostic factors associated with survival was limited by the relatively small sample sizes of these previous reports. We therefore used the Center for International Blood and Marrow Transplant Research (CIBMTR) database to compare clinical outcomes and factors associated with survival among a large cohort of AML patients whose leukemia relapsed following alloHCT.

METHODS

Data Source

We used the CIBMTR observational registry to compare clinical outcomes and factors associated with survival among AML patients whose leukemia relapsed following alloHCT between 1990 – 2010. The CIBMTR is a research organization combined with the National Marrow Donor Program (NMDP) and collects information from over 500 transplantation centers worldwide that prospectively report detailed information on consecutive transplants. To ensure data quality, a computerized system and scheduled data audits independently check all collected data based on specific disease forms provided by participating transplant centers. Privacy protections for patients participating in observational studies conducted by the CIBMTR are in compliance with all applicable federal regulations. Additionally, the CIBMTR ensures protected health information for all participants under the Health Insurance Portability and Accountability Act (HIPPA) Privacy Rule.

Patient Selection and Definitions

Adult and pediatric patients with AML relapsing after alloHCT were included in the study if they were in first or second complete remission (CR) when they received myeloablative or RIC alloHCT. Patients with *de novo* or secondary AML and patients receiving related donor (RD), unrelated donor (URD), or umbilical cord blood (UCB) donor grafts were included. Patients whose AML relapsed within the first 30 days of transplantation (n=64) or whose relapse date or conditioning regimens were unavailable for analysis (n=106) were excluded.

CR was defined as <5% bone marrow blasts with no morphological evidence of leukemia in the marrow or peripheral blood. Secondary AML was defined as leukemia arising from underlying myelodysplastic syndrome (MDS) or treatment-related AML (t-AML) due to previous chemotherapy or radiation. The Southwest Oncology Group cytogenetic classification was used for cytogenetic risk stratification as previously reported. (14) Intensive therapy was defined as induction-type cytoreductive chemotherapy with or without DLI and/or second allograft. HLA-typing for URD recipients was classified using published CIBMTR criteria.(15) Intensity of conditioning regimens were classified according to established CIBMTR definitions. (16, 17)

Study Endpoints and Statistical Analysis

The primary study endpoint was overall survival (OS) of AML patients relapsing after alloHCT. OS was defined as the time from relapse to death or last follow up for surviving patients. Secondary endpoints included clinical and disease prognostic factors of OS after post-transplantation relapse. Long-term survival was defined as survival ≥1 year after alloHCT relapse.

The Kaplan-Meier method was used to estimate OS probability. (18) Cox proportional hazards regression model was used to identify factors predictive of survival. The assumption of proportional hazards for each factor was tested by adding a time-dependent covariate. When the test indicated differential effects over time (non-proportional hazards), models were constructed breaking the post-transplantation time course into two periods, using the

maximized partial likelihood method to find the most appropriate breakpoint. A stepwise model selection approach was used to identify all significant risk factors predictive of survival. All statistical analysis was performed with SAS software (SAS Institute, Cary, NC, Version 9.2).

RESULTS

Patient Characteristics

We identified 1788 patients with AML relapsing after alloHCT from 286 CIBMTR centers and 43 countries. Of these, 413 patients survived ≥1 year after relapse (Table 1). Median time from transplantation to relapse was 7 months (range, 1–177 months), and median follow-up of survivors after post-transplantation relapse was 39 months (range, <1–193 months). Seventy percent of the patients underwent alloHCT in CR1. Median age of patients was 32 years (range, <1–76); 37% of patients were children (0–18 years old) and 39% were > 40 years old. Fifteen percent of patients had secondary AML, and 19% had unfavorable cytogenetics. A myeloablative conditioning regimen was used on over three-quarters of cases, and 52% of patients received a bone marrow graft. Donor types included HLA-identical RD (52%), well-matched URD (25%), UCB (13%), and mismatched URD (3%). Relapse within 6 months of transplantation occurred in 43% of patients, and isolated extramedullary relapse was rare (4%). AML relapse beyond 2 years of alloHCT occurred in only 18% of cases, and active GVHD prior to relapse was present in 41% of patients. The majority (n=1231, 69% of total) of patients received treatment for relapse, which included chemotherapy alone (37%), 2nd HCT with or without chemotherapy and/or DLI (21%), or DLI with or without chemotherapy (11%). However, only 15% of all patients achieved a subsequent CR. While 2nd HCT were rarely administered to those relapsing within 6 months, we found no association between use of intensive therapy and the time from HCT to relapse or the conditioning intensity of the 1st HCT.

Median time from HCT to relapse was 14 months for long-term survivors (> 1 year post relapse). Survivors living longer often received active treatment for relapse (79%), most frequently a 2nd HCT (44%), and commonly achieved subsequent CR (40%).

Management of Post-transplantation Relapse

A total of 267 patients received DLI for AML relapse, and DLI plus chemotherapy was used in 81% of them (Table 2). DLI was followed by 2nd HCT in 24% of patients treated with DLI. Median time from relapse to DLI was 2 months (<1–12 months), with 85% of patients receiving DLI within 6 months of leukemia relapse. Among all patients receiving DLI, 87 (32.6%) survived more than a year after leukemia relapse. The source of DLI was an HLA identical sibling donor for 61% of patients. Patients who received DLI and survived beyond 1 year often received subsequent 2nd HCT (34%).

A 2nd HCT was performed on 369 patients of whom 182 (49.3%) survived more than a year after relapse. The 2nd HCT conditioning regimens were myeloablative for 49%, RIC/or non-myeloablative (NMA) for 30%, and unknown for the rest of the patients. RD 2nd HCT was performed in about 1/2, URD in 1/3, UCB in 5% of the patients, and 2nd HCT donor source

was unknown for the rest of the cases. A different donor for the 2nd HCT was chosen in 45% of patients, but data on the donor was unavailable for 1/3 of patients. Median time from posttransplant leukemia relapse to the 2nd HCT was 3 months (<1–50 months), with the majority (81%) of relapses occurring within 6 months.

Among patients with evaluable status for response to therapy (n=846), subsequent CR was achieved in 29% of patients. DLI with or without chemotherapy (n=139) resulted in CR for 37% of cases; 2nd HCT with or without chemotherapy and/or DLI (n=264) resulted in CR for 44%; while chemotherapy alone (n= 443) induced CR in only 16%. Only rare remissions (6%) were observed among patients managed supportively.

Survival after Post-transplant Relapse

Median follow-up was 39 months after relapse (<1–193 months). Only 13% of all patients remained alive at the time of study analysis. Survival at 1 year after post-transplant relapse was 23%; however, survival probability at 3 years was only 4% for patients relapsing within 6 months of alloHCT, 12% for those relapsing within 6 month-2 years, 26% for 2–3 years, and 38% for 3+ years (Figure 1A). Adjusted probabilities of survival at 3 years were 13% for patients younger than 18 years, 17% for those 19–40 years old, and 8% for patients older than 41 years (Figure 1B). Median survival was 7 months (1–177 months) among patients receiving DLI and 12 months (1–150 months) among those receiving 2nd HCT. Cell-based therapy (DLI or 2nd HCT) resulted into significantly better ≥1 year post-relapse survival among patients relapsing 6 months and later post-HCT (Table 3). In multivariable analysis, a longer time from HCT to relapse (p<0.0001) and use of a RIC/NMA conditioning regimen (HR=0.77, p=0.0002) for the initial alloHCT were associated with better survival (Table 4). In contrast, age > 41 years (HR=1.42, p<0.0001), unfavorable cytogenetics (HR=1.37, p<0.0062), mismatched URD (HR=1.61, p<0.0008), UCB (HR=1.23, p<0.0078), and presence of active GVHD at relapse (HR=1.25, p<0.0001) were independent predictors of inferior survival.

Relapse or persistent leukemia was the primary cause of death in 71% of cases. While relapse was the cause of death in 80% of patients surviving less than a year, only 42% of longer surviving patients died of leukemia. Infection (4%) followed by GVHD (3%) and organ failure (3%) were the next most frequent causes of death and were similar in longer and shorter survivors.

DISCUSSION

In the 1788 AML patients relapsing after myeloablative or RIC/NMA alloHCT we found that survival after post-transplant relapse was significantly influenced by time from HCT to relapse, patients' age, cytogenetic risk group, donor type, HLA matching and conditioning intensity. Although similar to prior reports we observed poor survival following AML relapse after alloHCT, (1, 2, 5, 7, 11, 19) longer remission after the initial alloHCT was an independent predictor of better survival. Patients who remained in remission ≥3 years after HCT had promising survival even after late relapse. In contrast, patients whose AML relapsed within 6 months of alloHCT had dismal survival, as observed in prior reports.(1, 5) We also observed favorable survival after relapse in those receiving a 2nd HCT with or

without chemotherapy and/or DLI, particularly those achieving CR; this outcome is also consistent with prior reports. (1, 5, 19)

Other prognostic factors associated with survival after post-alloHCT relapse were patient age, active GVHD at the time of relapse, cytogenetic risk group, donor type/HLA matching, and conditioning intensity. Older patients are more likely to be unfit at the time of relapse, unable to tolerate further intensive therapy, and are more likely to be managed supportively. The 37% of our patients who were children were more likely to receive further intensive therapy and survive longer. Similarly, active GVHD at the time of relapse precludes the use of potentially valuable cell-based therapy and might increase the risk of infectious complications. Poor survival was seen with partially matched URD and UCB transplants. (7) Without the option of DLI for UCB patients, the only potential curative option for these patients remains a 2nd HCT, but this was rarely performed. Somewhat surprisingly, RIC/NMA conditioning at 1st HCT was associated with better survival independent of patient age and time from transplant to relapse. Previous reports of single-institution studies have made similar observations. (5, 7) We speculate that the lower risks of post-HCT morbidity after RIC/NMA conditioning may allow these patients to be better candidates for subsequent intensive therapy versus those treated with more intensive myeloablative alloHCT. It is also possible that leukemia relapse after RIC/NMA conditioning may remain more sensitive to chemotherapy than after myeloablative conditioning and subsequently contribute to a better clinical outcome.

We had no available data to assess the influence of tumor burden at the time of relapse on subsequent response to therapy and survival. In addition, we were unable to systematically analyze the impact of each therapeutic approach on subsequent clinical outcomes because these were intermediate events occurring after relapse and data reporting was incomplete. Additionally, we were unable to directly assess the effect of immunosuppression withdrawal on achievement of remission; however, all previous reports suggest that this approach alone has minimal, if any, therapeutic benefit. (7, 20)

In conclusion, relapse of AML after alloHCT predicted poor outcomes. We recommend that patients with longer remission after initial alloHCT be considered for 2nd HCT or chemotherapy plus DLI, as this approach was associated with prolonged survival in our cohort. Patients who relapse early, are elderly, or have active GVHD at the time of relapse are unlikely to benefit from intensive therapy and might best be managed supportively. Beyond compassionate supportive care, new approaches including prevention strategies (21) are needed for patients with early relapse after alloHCT.

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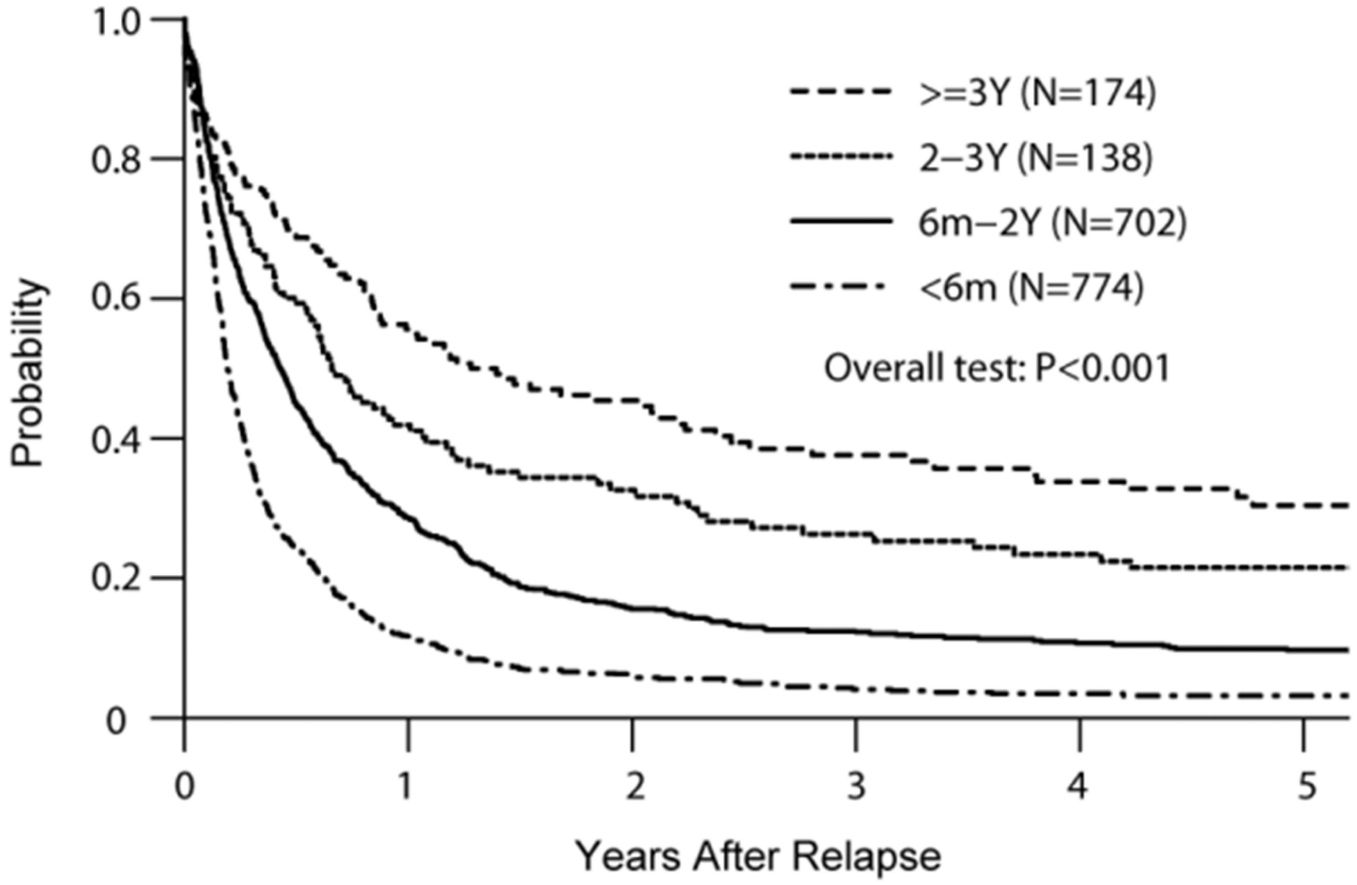

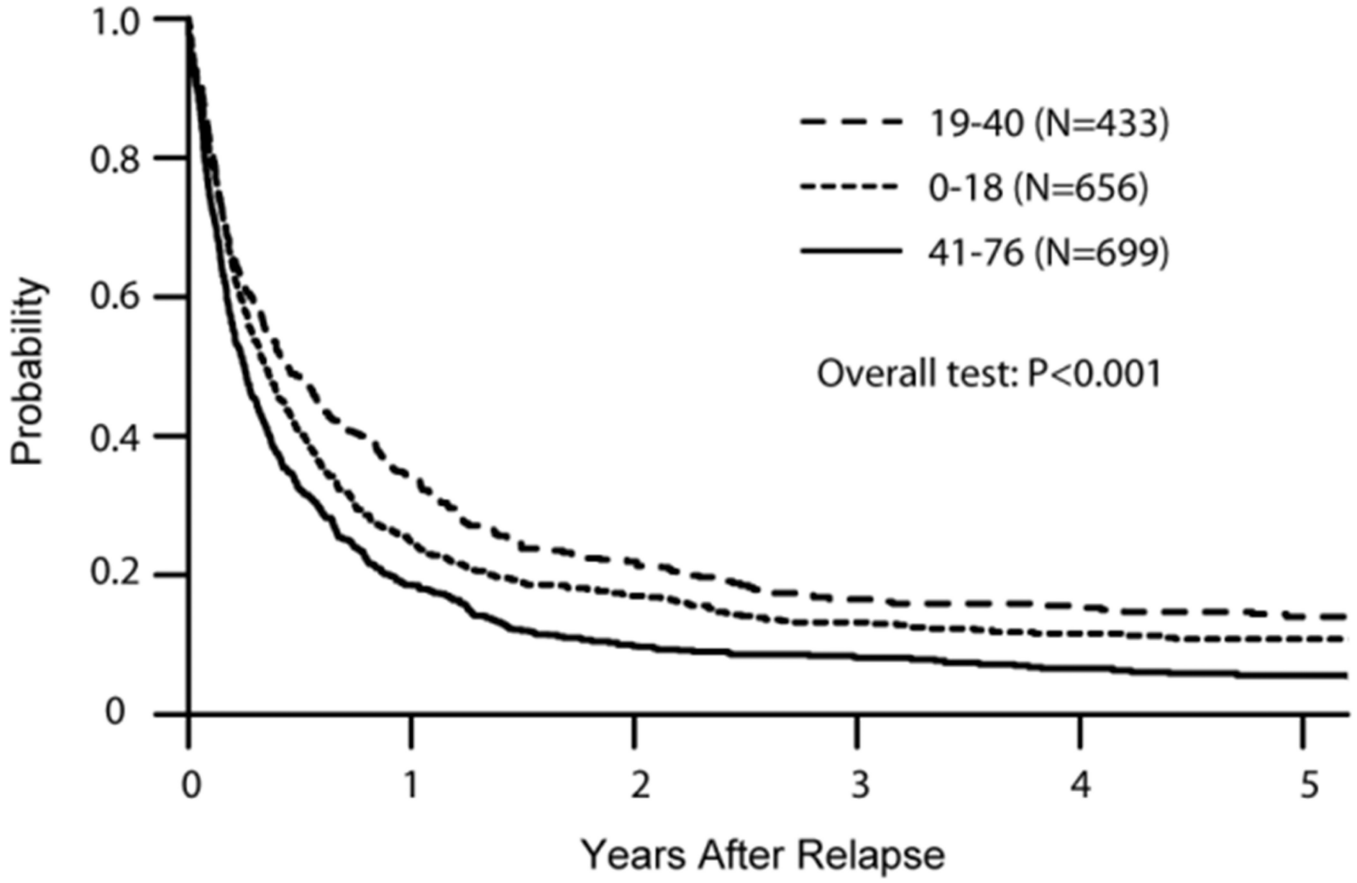

Figure 1.

A: Adjusted Overall Survival by Time from HCT to Relapse

B: Adjusted Overall Survival by Age

Table 1

Patient characteristics

Variable	Total N (%)	Survival ≥ 1 year post relapse N (%)
Number of patients	1788	413
Year of HCT		
1990–2000	745 (42)	203 (49)
2001–2010	1043 (59)	210 (51)
HCT during CR1	1249 (70)	312 (76)
CR2	539 (30)	101 (24)
Age		
Median (range)	32 (<1–76)	30 (1–75)
0–18y	613 (34)	136 (33)
19–40y	439 (25)	138 (33)
41–76y	736 (41)	139 (34)
AML type		
De novo	1450 (81)	348 (84)
Secondary	276 (15)	47 (11)
Missing	62 (3)	18 (4)
Cytogenetics scoring		
Favorable	138 (8)	45 (11)
Intermediate / normal	805 (45)	190 (46)
Unfavorable	334 (19)	52 (13)
Missing	511 (29)	126 (31)
Myeloablative	1374 (77)	337 (82)
RIC/NMA	414 (23)	76 (18)
Graft type		
Bone marrow	935 (52)	240 (58)
Peripheral blood	621 (35)	138 (33)
Cord blood	232 (13)	35 (8)
Donor type		
HLA-id sibling	936 (52)	245 (59)
URD well matched	317 (18)	69 (17)
URD partially matched	134 (7)	35 (8)
URD mismatched	56 (3)	7 (2)
URD unknown	113 (6)	22 (5)
Cord blood	232 (13)	35 (8)
GVHD prophylaxis		
ATG/alemtuzumab	406 (23)	80 (19)
Ex-vivo T cell depletion	48 (3)	12 (3)
CSA/tac ± other	1334 (75)	321 (78)
Time from HCT to relapse		
Median (range)	7 (1–177)	14 (1–177)

Variable	Total N (%)	Survival ≥ 1 year post relapse N (%)
< 6m	774 (43)	88 (21)
6m–2y	702 (39)	191 (46)
2–3y	138 (8)	52 (13)
≥3y	174 (10)	82 (20)
AML relapse site		
Extramedullary only	80 (4)	25 (6)
Bone Marrow ± other sites	1046 (59)	200 (48)
Not reported/missing	662 (37)	188 (44)
Active GVHD prior to relapse		
Yes	727 (41)	170 (41)
No	1028 (57)	234 (57)
Missing	33 (2)	9 (2)
Treatment for relapse		
2nd HCT±chemo±DLI	369 (21)	182 (44)
DLI±chemo	202 (11)	57 (14)
Chemo only	660 (37)	87 (21)
Supportive care/no therapy	357 (20)	35 (8)
Missing	200 (11)	52 (13)
Response to therapy		
CR	271 (15)	165 (40)
No response	704 (39)	121 (29)
Missing	813 (45)	127 (31)
Surviving at last follow-up	229 (13)	173 (42)
Median follow-up after relapse, months	39 (<1–193)	59 (12–193)

Table 2

Characteristics of patients treated with DLI and/or 2nd HCT

Variable	Total N (%)	Survival ≥ 1 year post relapse N (%)
DLI±2nd HCT	267	87
DLI+chemotherapy		
Yes	216 (81)	75 (86)
No	51 (19)	12 (14)
DLI‡+2nd HCT		
+2nd HCT	65 (24)	30 (34)
No 2nd HCT	202 (76)	57 (66)
Type of donor		
HLA-identical sibling	162 (61)	59 (68)
Unrelated	102 (38)	26 (30)
Missing	3 (1)	2 (2)
Donor Gender		
Male	144 (54)	46 (53)
Female	105 (39)	38 (44)
Missing	18 (7)	3 (3)
Time from relapse to DLI		
Median (range)	2 (<1–12)	2 (<1–12)
≤6m	226 (85)	70 (80)
>6m	11 (4)	5 (6)
Missing	25 (9)	9 (10)
2nd HCT	369	182
Conditioning		
MA	181 (49)	99 (54)
RIC/NMA	110 (30)	57 (31)
Missing	78 (21)	26 (14)
Donor type of 2nd HCT		
Related	197 (53)	94 (52)
Unrelated	127 (34)	70 (38)
Cord Blood	20 (5)	9 (5)
Missing	25 (7)	9 (5)
Donor gender		
Male	168 (46)	78 (43)
Female	126 (34)	67 (37)
Missing	75 (20)	37 (20)
Same donor as 1st HCT		
No	81 (22)	49 (27)
Yes	166 (45)	73 (40)

Variable	Total N (%)	Survival ≥ 1 year post relapse N (%)
Missing	122 (33)	60 (33)
Time from relapse to 2nd HCT		
Median (range)	3 (<1–50)	3 (<1–50)
≤6m	299 (81)	135 (74)
>6m	52 (14)	40 (22)
Missing	18 (5)	7 (4)

‡Reflects DLI with or without chemotherapy

Table 3

Survival after DLI and 2nd HCT

Time from HCT to relapse	DLI			2nd HCT		
	N	Survival ≥ 1 year post relapse N (%)	*p*-value£	N	Survival ≥ 1 year post relapse N (%)	*p*-value£
<6 months	90	12 (13)	<0.001	110	35 (32)	<0.001
6 months–2 years	81	28 (35)		167	92 (55)	
2 – 3 years	14	7 (50)		37	23 (62)	
≥ 3 years	17	10 (59)		55	32 (58)	
Median (range)	7 (1–177)*	13 (2–106)		12 (1–150)†	14 (2–78)	

£*p*-value reflects the time from HCT to relapse

*Median survival of all patients receiving DLI

†Median survival of all patients receiving 2nd HCT

Table 4

Factors influencing survival of AML patients relapsing after alloHCT

		Univariate		Multivariate	
Variable	**N**	**RR (95% CI)**	***P*-value**	**RR (95% CI)**	***P*-value**
Time from HCT to relapse			<0.0001		<0.0001
< 6m	774	1.00		1.00	
6m-2y	702	0.60 (0.53–0.66)	<0.0001	0.55 (0.50–0.62)	<0.0001
2–3y	138	0.40 (0.33–0.50)	<0.0001	0.39 (0.32–0.49)	<0.0001
≥ 3y	174	0.30 (0.24–0.37)	<0.0001	0.28 (0.23–0.35)	<0.0001
Year of HCT					
1990–2000	745	1.00		NS	NS
2001–2010	1043	1.19 (1.08–1.32)	0.0006		
Age			<0.0001		<0.0001
≤ 18y	656	1.00		1.00	
19–40y	433	0.86 (0.75–0.98)	0.02	1.00 (0.87–1.15)	0.10
≥41y	699	1.27 (1.13–1.42)	<0.0001	1.42 (1.24–1.64)	<0.0001
Gender					
Male	988	1.00		NS	NS
Female	800	0.98 (0.88–1.08)	0.63		
Cytogenetics			<0.0001		0.02
Favorable	138	1.00		1.00	
Intermediate/Norm	805	1.27 (1.04–1.56)	0.02	1.15 (0.94–1.41)	0.18
Unfavorable	334	1.64 (1.32–2.04)	<0.0001	1.37 (1.09–1.71)	0.01
Unknown	511	1.22 (0.99–1.51)	0.06	1.13 (0.91–1.39)	0.27
Conditioning					
MA	1374	1.00		1.00	
RIC/NMA	414	1.18 (1.05–1.33)	0.01	0.77 (0.66–0.88)	0.0002
Donor Type			<0.0001		0.0007
RD/URD-Matched	1387	1.00		1.00	
URD-Mismatched	56	1.65 (1.25–2.17)	0.0003	1.61 (1.22–2.13)	0.0008
URD-Unknown	113	1.10 (0.90–1.35)	0.37	1.10 (0.89–1.36)	0.37

		Univariate		Multivariate	
Variable	**N**	**RR (95% CI)**	***P*-value**	**RR (95% CI)**	***P*-value**
Cord Blood	232	1.38 (1.19–1.60)	<0.0001	1.23 (1.06–1.42)	0.01
Active GVHD at relapse			0.20		0.0002
No	1028	1.00		1.00	
Yes	727	1.10 (0.99–1.21)	0.07	1.25 (1.13–1.39)	<0.0001
Unknown	33	1.01 (0.70–1.47)	0.95	1.05 (0.72–1.52)	0.80