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Association of Second Allogeneic Hematopoietic Cell Transplant vs Donor Lymphocyte Infusion With Overall Survival in Patients With Acute Myeloid Leukemia Relapse

Mohamed A. Kharfan-Dabaja, MD, MBA; Myriam Labopin, MD, PhD; Emmanuelle Polge, MSc; Taiga Nishihori, MD; Ali Bazarbachi, MD, PhD; Jürgen Finke, MD; Michael Stadler, MD, PhD; Gerhard Ehninger, MD; Bruno Lioure, MD; Nicolaas Schaap, MD, PhD; Boris Afanasyev, MD, PhD; Moshe Yeshurun, MD; Cecilia Isaksson, MD; Johan Maertens, MD, PhD; Yves Chalandon, MD, PhD; Christoph Schmid, MD; Arnon Nagler, MD, MSc; Mohamad Mohty, MD, PhD

IMPORTANCE The optimal treatment approach to patients with acute myeloid leukemia (AML) who relapse after an allogeneic hematopoietic cell transplant (allo-HCT) remains elusive. No randomized clinical trial comparing survival outcomes of a second allo-HCT (allo-HCT2) vs donor lymphocyte infusion (DLI) has been conducted to date.

OBJECTIVE To compare overall survival (OS) after an allo-HCT2 or DLI in relapsed AML after a first allo-HCT.

DESIGN, SETTING, AND PARTICIPANTS A retrospective registry study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation involving 418 adults who received an allo-HCT2 (n = 137) or DLI (n = 281) for postallograft-relapsed AML. Analysis was assessed on the principle of intent-to-first received intervention. The data were collected from November 21, 2015, to May 15, 2017, and analysis was performed June 1, 2017.

MAIN OUTCOMES AND MEASURES Number of patients with relapsed AML who are alive after 2 years and 5 years from receiving an allo-HCT2 or DLI.

RESULTS Of the 418 patients, 228 (54.5%) were men; mean age was 46.2 years (interquartile range, 36.5-56.9 years). There was no apparent difference in OS whether an allo-HCT2 or DLI was prescribed (2-year OS with allo-HCT2, 26%; 5-year OS with allo-HCT2, 19%; 2-year OS with DLI, 25%; 5-year OS with DLI, 15%; $P = .86$). Overall survival was better if either of these procedures was offered when the patient was in complete remission (hazard ratio, 0.55; 95% CI, 0.41-0.74; $P < .001$). Conversely, OS was low for patients relapsing within less than 6 months after an allo-HCT1, regardless of the treatment prescribed (5-year OS: allo-HCT2, 9%; 95% CI, 1%-17% vs DLI, 4%; 95% CI, 1%-8%; $P = .86$).

CONCLUSION AND RELEVANCE Heterogeneity of the patient-, disease-, and treatment-related characteristics limit the ability to recommend one approach over another. Findings of this study highlight that best outcomes seem to be achieved in patients relapsing 6 or more months from an allo-HCT1 or those in complete remission at the time of either allo-HCT2 or DLI.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Mohamad Mohty, MD, PhD, Hôpital Saint Antoine, Hematology Department, Université Pierre et Marie Curie (UPMC), Paris, France (mohamad.mohty@inserm.fr).

Growing understanding of molecular aspects of acute myeloid leukemia (AML) revealed an increasingly heterogeneous disease and challenged traditional treatment algorithms that relied solely on clinical and cytogenetic characteristics.[1-3] Although new therapies have been added to the armamentarium of AML management,[4,5] the disease remains incurable, particularly when adverse risk features are present and in patients with relapsed and/or refractory AML.[6] Allogeneic hematopoietic cell transplant (allo-HCT) is potentially curative in AML. However, outcomes are largely dependent on remission status at the time of allografting, with anticipated overall survival (OS) rates of 15% to 30% in relapsed/refractory disease or primary induction failure[7,8] and 50% to 75% in patients who receive allografts during the first complete remission (CR).[9-11] However, relapse still occurs in 25% to 30% of the cases, even when myeloablative regimens are used.[10-12]

Treatment options for AML relapsing after an allo-HCT are limited. Patients with significant toxic effects from the first allo-HCT (allo-HCT1) are generally offered supportive care, and those deemed eligible for intensive interventions receive an allo-HCT2 or donor lymphocyte infusion (DLI). A retrospective analysis from the European Society for Blood and Marrow Transplantation (EBMT) comparing outcomes of AML relapsing after an allo-HCT1 among those who did or did not receive DLI showed improved 2-year OS with DLI (21% vs 9%, $P < .001$).[13] Alternatively, Orti et al[14] described outcomes of 116 patients (76% AML) who received an allo-HCT2 showing a 5-year OS of 32%; presence of active disease and a shorter time from first to second allo-HCT indicated a likely poor disease-free survival.

To our knowledge, there have been no randomized clinical trials comparing allo-HCT2 with DLI in AML relapsing after an allo-HCT1. The decision to offer either option is based on several factors, including donor availability, remission status, presence of disabling comorbidities, and center or physician preference. The primary objective of this study was to compare OS after an allo-HCT2 or 1 or more DLIs in relapsed AML after an allo-HCT1.

Key Points

Question Does a treatment approach using a second allogeneic hematopoietic cell transplant compared with donor lymphocyte infusion yield superior overall survival for acute myeloid leukemia relapse after a first allogeneic hematopoietic cell transplant?

Findings In this registry-based study of 418 adults, comparable overall survival was achieved with both allogeneic hematopoietic cell transplant and donor lymphocyte infusion at 2 years (26% vs 25%) and 5 years (19% vs 15%). A shorter time from the first allogeneic hematopoietic cell transplant to relapse and presence of active disease at the time of allogeneic hematopoietic cell transplant or donor lymphocyte infusion were adverse prognostic factors for overall survival.

Meaning Allogeneic hematopoietic cell transplant or donor lymphocyte infusion appear to offer the best results in patients relapsing after 6 months from allogeneic hematopoietic cell transplant or those who attain complete remission beforehand.

Methods

Study Design and Patient Population

This was a retrospective observational study of patients reported to the Acute Leukemia Working Party of the EBMT with completed follow-up. The EBMT is a voluntary working group of more than 500 transplant centers that are required to report all consecutive HCTs and follow-up once a year. The validation and quality control program includes verification of computer printouts of entered data, cross-checking with national registries, and on-site visits of selected teams. This study was approved by the Acute Leukemia Working Party of the EBMT institutional review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.[15] All patients provided written informed consent authorizing use of information for research purposes.

Eligibility criteria entailed adults (age ≥18 years) who received an allo-HCT1 in CR between 1992 and 2015 for de novo or secondary AML. There was no preset upper age limit. The cell source for an allo-HCT1 was limited to either bone marrow or peripheral blood stem cells. Eligible patients for the DLI cohort must have received this treatment for the sole purpose of treating relapse.

A total of 2032 patients were identified as potentially eligible. In addition to routinely available data existing in the Acute Leukemia Working Party registry, centers were asked to report information regarding treatment of AML relapsing after an allo-HCT1 by using an allo-HCT2 or DLI. Data collected at the time of allo-HCT1 are summarized in eTable 1 in the Supplement. **Table 1** reports data collected at the time of allo-HCT2 or DLI.

Data collection was performed from November 21, 2015, until May 15, 2017. Sixty-three centers agreed to participate, and questionnaires were completed for 530 patients. However, 112 patients were excluded for not meeting inclusion criteria or not having information on the key risk factors integrated into the analysis. Final analysis included 418 patients who underwent transplant at 1 of 61 EBMT centers. Survival data were updated as of May 1, 2017. Completeness to follow-up post intervention was 96.2% (2-year), 87.7% (5-year), and 86.6% at date of analysis (June 1, 2017).

Statistical Analysis

Patient-, disease-, and treatment-related variables of the groups (allo-HCT2 vs DLI) were compared using χ^2 or Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. Baseline characteristics were summarized using median, interquartile range, and range for continuous measures and numbers and frequencies for categorical measures.

The primary end point was OS. Secondary end points included leukemia-free survival (LFS), relapse incidence (RI), non-relapse mortality (NRM), grade 2 to 4 acute graft vs host disease (aGVHD), chronic GVHD (cGVHD), and relapse-related deaths.

Table 1. Patient-, Disease-, and Treatment-Related Characteristics

Variable	DLI (n = 281)[a]	Allo-HCT2 (n = 137)[b]	*P* Value
Age at intervention, median (range [IQR]), y	49 (19-75 [39-59])	43 (18-67 [32-52])	<.001
Sex, No. (%)			
Male	153 (54.4)	75 (54.7)	.95
Female	128 (45.6)	62 (45.3)	
Donors, No. (%)			
Male	189 (68.2)	84 (62.2)	.23
Female	88 (31.8)	51 (37.8)	
Missing/unknown	4	2	
Median year of allo-HCT1	2007	2006	.03
IQR	2004-2011	2003-2008	
Range	1992-2014	1996-2014	
Median year of relapse	2008	2008	.23
IQR	2005-2012	2005-2011	
Range	1999-2015	2000-2014	
Median year of intervention	2008	2008	.37
IQR	2005-2012	2005-2011	
Range	1999-2015	2000-2014	
Same original donor, No. (%)			
Yes	274 (100)	73 (59.8)	<.001
No	NA	49 (40.2)	
Missing/unknown	7	15	
Remission status at intervention, No. (%)			
CR2	36 (12.8)	46 (33.6)	<.001
CR3	15 (5.3)	7 (5.1)	
Relapse 1	183 (65.1)	73 (53.3)	
Relapse 2	47 (16.7)	11 (8.0)	
Donor source, No. (%)			
MRD	149 (53.6)	76 (55.5)	.11
URD	129 (46.4)	59 (43.1)	
Haploidentical	0	2 (1.5)	
Missing/unknown	3	0	
Cell source, No. (%)			
BM	13 (4.7)	6 (4.4)	.36
PBSC	263 (95.3)	130 (94.9)	
BM+PBSC	0	1 (0.7)	
Missing/unknown	5	0	
Time from allo-HCT1 to relapse, median (range [IQR]), d	211 (20-3872 [117-453])	348 (30-4569 [134-712])	.004
Time from allo-HCT1 relapse to intervention, median (range [IQR]), d	30 (0-305 [15-69])	71 (6-311 [39-119])	<.001
Grade 2-4 aGVHD prior to intervention, No. (%)			
Yes	23 (8.3)	24 (17.9)	.004
No	255 (91.7)	110 (82.1)	
Missing/unknown	3	3	
cGVHD (any grade) prior to intervention, No. (%)			
Yes	60 (22.6)	32 (24.6)	.66
No	205 (77.4)	98 (75.4)	
Missing/unknown	16	7	
Cytotoxic therapy, including hypomethylating agents prior to DLI, No. (%)			
Yes	171 (64.0)	NA	
No	96 (36.0)	NA	
Missing/unknown	14	NA	

(continued)

Table 1. Patient-, Disease-, and Treatment-Related Characteristics (continued)

Variable	DLI (n = 281)[a]	Allo-HCT2 (n = 137)[b]	*P* Value
Regimen used for allo-HCT2, No. (%)			
MAC	NA[c]	46 (35.1)	
RIC	NA[c]	85 (64.9)	
Missing/unknown	NA[c]	6	

Abbreviations: aGVHD, acute graft-vs-host disease; allo-HCT1, first allogeneic hematopoietic cell transplant; allo-HCT2, second allogeneic HCT; BM, bone marrow cells; cGVHD, chronic GVHD; CR2, second complete remission; CR3, third complete remission; DLI, donor lymphocyte infusion; IQR, interquartile range; MAC, myeloablative conditioning regimen; MRD, human leukocyte antigen–matched related donor; NA, not applicable; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning regimen; URD, unrelated donor.

[a] DLI only, 230; DLI and allo-HCT2, 51.

[b] Allo-HCT2 only, 135; allo-HCT2 and DLI, 2.

[c] The regimens used were not factored in the intent-to-first intervention analysis.

Outcomes were evaluated on the principle of intent-to-first received intervention. In addition, we analyzed the subgroup who received either DLI or HCT2 only, excluding those who received both treatments.

Definitions

For the purpose of evaluating response, CR represents complete hematologic remission. Alternatively, AML relapse represents evidence of circulating myeloblasts or 5% or more bone marrow infiltration. *Overall survival* was defined as time from intervention to death, regardless of cause. *Leukemia-free survival* was defined as survival without evidence of relapse or progression. *Relapse incidence* was defined as leukemia recurrence (any site). As the exact date of progression for patients who received the intervention in active disease and never achieved CR was not available, LFS and RI were evaluated only in patients known to be in CR. *Nonrelapse mortality* was defined as death without evidence of relapse or progression. *Conditioning regimen intensity* (myeloablative conditioning or reduced-intensity conditioning) was defined based on established criteria[16]; nonmyeloablative regimens were included within the broader reduced-intensity conditioning rubric.

Statistical Methods

All surviving patients were censored at the time of last contact. Cumulative incidence curves were used for RI and NRM in a competing risk setting because death and relapse are competing events. Moreover, to assess cumulative incidence of aGVHD (day +100) and cGVHD (1 – year), we considered relapse and death as competing events. All transplant-related deaths were competing events when studying relapse-related deaths. Probabilities of OS and LFS (patients in CR) were calculated using the Kaplan-Meier method. Cumulative incidence was used to estimate the end points of RI, NRM, aGVHD, and cGVHD to accommodate for competing risks.[17]

Univariable analyses were performed using the Gray test[18] for cumulative incidence functions (RI and NRM) and the log-rank test for OS and LFS. Multivariable analyses were performed using the Cox proportional hazards regression model, including variables with unbalanced distribution between the groups or adjusted for variables known as potentially influencing outcome. We did not include T-cell depletion as a variable because its use is largely related to donor source (predominantly when using unrelated/mismatched donors). Continuous variables were categorized according to the median for univariable analyses and included without categorization in the Cox proportional hazards regression model. Patients with missing information were excluded from the analyses. Results were expressed as the hazard ratio (HR) with 95% CIs. Type I error rate was fixed at .05 for determination of factors associated with time-to-event outcomes. All *P* values were 2-sided. Statistical analyses were performed with SPSS, version 22.0 (SPSS Inc) and R, version 3.2.3 5 (https://www.R-project.org/).

Results

The median number of reported cases per center was 5 (range, 1-55). Patient-, disease-, and treatment-related characteristics at the time of allo-HCT1 are given in eTable 1 in the Supplement.

All consecutive patients who met inclusion criteria (n = 418) were included. Of these, 228 (54.5%) were men; mean age was 46.2 years (interquartile range, 36.5-56.9). The allo-HCT2 group comprised 137 patients (allo-HCT2 only, 135; allo-HCT2 + DLI, 2) with a median age of 43 (range, 18-67) years and the DLI group included 281 patients (DLI only, 230; DLI + allo-HCT2, 51) whose median age was 49 (range, 19-75) years ($P < .001$). Patients who underwent allo-HCT2 were less likely to receive treatment from the original donor (59.8% vs 100%; $P < .001$); however, they had a higher incidence of remission (CR2 or CR3) at the time of intervention (38.7% vs 18.1%; $P < .001$). In allo-HCT2 recipients, relapse occurred at a later time from allo-HCT1 (348 vs 211 days; $P = .004$) and intended therapy was, consequently, administered later (71 vs 30 days; $P < .001$). Also, patients who underwent allo-HCT2 were more likely to have experienced grade 2 to 4 aGVHD before intervention (17.9% vs 8.3%; $P = .004$), but the incidence of prior cGVHD (any grade) was similar between the groups (24.6% vs 22.6%; $P = .66$). These and other characteristics are summarized in Table 1.

Donor Chimerism

Data on donor chimerism were available for 101 of 137 patients (73.7%) who received an allo-HCT2: complete (n = 37), mixed/partial (n = 54), and lost (n = 10). For DLI recipients, donor chimerism results were available for 227 of 281 patients (80.8%):

complete (n = 76), mixed/partial (n = 141), and lost (n = 10). The difference between the groups was not significant (*P* = .10). These results, however, did not necessarily represent the donor chimerism status immediately before allo-HCT2 or DLI but rather reflected testing at any time during the posttransplant period after an allo-HCT1 and before an allo-HCT2 or DLI.

DLI Doses and Frequency of Administration

Data on first-administered CD3 cell dose (× 10^6/kg recipient weight) were available for 225 of 281 cases (80.1%). Median dose was 6.6 × 10^6 cells/kg (range, 0.05-840 × 10^6 cells/kg; IQR, 1-20 × 10^6 cells/kg).

The number of administered infusions for 248 of 281 patients (ie, available in 88.3%) cases was: 1 infusion (n = 123), 2 (n = 61), 3 (n = 33), 4 (n = 14), 5 (n = 7), 6 (n = 5), 7 (n = 2), 8 (n = 1) and 11 (n = 2). A schedule of DLI administration could be evaluated for 148 of 281 cases (52.7%). Donor lymphocyte infusions were administered at a fixed-dose in 50 patients and in an escalating schedule in 98 patients.

Outcomes

Median follow-up from day of intervention for all surviving patients was 63 (range, 1-157) months. For the allo-HCT2 group, median follow-up of survivors was 61 (15-110) months; for the DLI group, it was 64 (range, 1-157) months.

A higher proportion of allo-HCT2 recipients was in CR at the time of intervention and remained so afterward (53 [38.7%] vs 51 [18.1%]; *P* < .001). Also, a higher proportion of patients in the allo-HCT2 group who were not in CR at the time of intervention achieved CR afterward (53 [38.7%] vs 68 [24.2%]; *P* < .001) (**Table 2**).

There was no significant difference in OS between the groups regardless of remission status at the time of intervention (all patients) (**Figure 1**, Table 2) or in patients who were in CR when receiving allo-HCT2 or DLI (eFigure 1 in the Supplement).

We compared the OS of patients who relapsed within less than 6 months from allo-HCT1 and received an allo-HCT2 (n = 46) or DLI (n = 121). Two-year OS for an allo-HCT2 was 11% (95% CI, 2%-20%) and, for DLI, 9% (95% CI, 4%-14%). The 5-year OS for an allo-HCT2 or DLI was 9% (95% CI, 1%-17%) and 4% (95% CI, 1%-8%), respectively (*P* = .86) (Table 2).

We also compared the OS of patients who relapsed 6 months or more after an allo-HCT1 and received an allo-HCT2 (n = 91) or DLI (n = 160). Two-year OS for allo-HCT2 was 34% (95% CI, 24%-43%) and for DLI, 37% (95% CI, 30%-45%). The 5-year OS for allo-HCT2 or DLI was 24% (95% CI, 14%-33%) and 23% (95% CI, 16%-30%), respectively (*P* = .53) (Table 2).

Within the group of patients who received an allo-HCT2, 2-year OS was better in patients in CR: 35% (95% CI, 22%-48%) vs 20% (95% CI, 11%-29%) (*P* = .02) (**Figure 2**A). The presence of CR vs active disease prior to DLI also yielded better 2-year OS (51%; 95% CI, 36%-65% vs 19%; 95% CI, 14%-25%; *P* < .001) (Figure 2B).

There was no significant difference in LFS between patients who were in CR at the time of allo-HCT2 or DLI (Table 2; eFigure 2 in the Supplement). The 2-year LFS for allo-HCT2 was 20% (95% CI, 9%-31%) and, for DLI, 38% (95% CI, 24%-52%) (*P* = .17).

There was no significant difference in RI in patients who were in CR at the time of allo-HCT2 or DLI (Table 2). The 2-year RI for allo-HCT2 was 54% (95% CI, 39%-66%) and, for DLI, 49% (95% CI, 34%-62%) (*P* = .64).

Patients in the allo-HCT2 group (vs DLI) had a higher incidence of NRM whether the analysis included all or only patients who received the intended therapy with active disease (Table 2). For patients in CR at the time of allo-HCT2 or DLI, the NRM was similar (Table 2).

Allo-HCT2 patients had a higher incidence of grade 2 to 4 aGVHD at day +100 post transplantation when evaluating all cases, regardless of remission status (Table 2). Alternatively, the incidence of day +100 grade 2 to 4 aGVHD was similar between the groups when the analysis was restricted to patients in CR (Table 2). Patients treated with allo-HCT2 or DLI had a similar incidence of 1-year cGVHD (any grade) whether the analysis was conducted on all patients, regardless of remission status, or only in those in CR (Table 2).

Death from relapse occurred in 64 (55.7% of total deaths) patients in the allo-HCT2 and 179 (75.8%) in the DLI group (Table 2). The DLI recipients had significantly higher relapse-related deaths at 2 years (59%; 95% CI, 53%-65% vs 40%; 95% CI, 32%-48%) and at 5 years (66%; 95% CI, 60%-72% vs 46%; 95% CI, 40%-54%) post transplantation (*P* = .001).

A 2-fold higher proportion of deaths due to NRM was reported in allo-HCT2 recipients (44% vs 24%). Infections and GVHD represented the 2 most common causes of death in the 2 groups (eTable 2B in the Supplement).

Multivariable Analysis

Complete remission at the time of intervention (HR, 0.55; 95% CI, 0.41-0.74; *P* < .001), prior cGVHD (HR, 0.71; 95% CI, 0.53-0.95; *P* = .02), and a longer time after an allo-HCT1 to relapse (HR, 0.99; 95% CI, 0.98-0.99; *P* < .001) resulted in better OS when analysis included all patients regardless of remission status. Poor-risk cytogenetics and prior aGVHD were associated with worse OS (eTable 3 in the Supplement).

For NRM, prior aGVHD resulted in worse NRM (eTables 3 and 4 in the Supplement). Moreover, for patients in CR at the time of intervention, NRM was adversely affected when donors other than human leukocyte antigen–matched related donors were used (eTable 4 in the Supplement).

Using Same vs Different Donors When Offering an Allo-HCT2

Data comparing the effect of donor source were available in 122 patients (same donor, 73; different donor, 49). There was no significant difference in 2-year OS (same, 25%; 95% CI, 15%-34% vs different, 28%; 95% CI, 15%-41%; *P* = .49) or 2-year NRM (same, 23%; 95% CI, 14%-34% vs different, 31%; 95% CI, 18%-44%; *P* = .38). Moreover, a comparison limited to 46 patients in CR at the time of allo-HCT2 (same, 27; different, 19) did not show a significant difference in 2-year OS (same, 41%; 95% CI, 22%-59% vs different, 41%; 95% CI,

Table 2. Treatment Outcomes of DLI vs Allo-HCT2

Outcome	% (95% CI) DLI	% (95% CI) Allo-HCT2	*P* Value
Response, No. (%)			
CR before and after intervention	51 (18.1)	53 (38.7)	<.001
CR after intervention	68 (24.2)	53 (38.7)	
No response	160 (56.9)	22 (16.1)	
Not available[a]	2 (0.1)	9 (6.6)	
OS all patients			
2 y	25 (20-30)	26 (19-33)	.86
5 y	15 (10-19)	19 (12-25)	
OS: pts in CR received intervention			
2 y	51 (36-65)	35 (22-48)	.22
5 y	33 (19-48)	29 (17-42)	
OS: regardless of remission status			
Relapse <6 mo from allo-HCT1[b]			
2 y	9 (4-14)	11 (2-20)	.86
5 y	4 (1-8)	9 (1-17)	
Relapse ≥6 mo from allo-HCT1[c]			
2 y	37 (30-45)	34 (24-43)	.53
5 y	23 (16-30)	24 (14-33)	
OS: pts with active disease received intervention			
2 y	19 (14-25)	20 (11-29)	.59
5 y	11 (7-15)	11 (4-18)	
LFS: pts in CR received intervention			
2 y	38 (24-52)	20 (9-31)	.17
5 y	21 (8-33)	18 (7-28)	
Relapse: pts in CR received intervention			
2 y	49 (34-62)	54 (39-66)	.64
5 y	64 (47-77)	56 (41-68)	
NRM: all patients			
2 y	9 (6-13)	26 (19-34)	<.001
5 y	10 (7-14)	29 (21-36)	
NRM: pts in CR received intervention			
2 y	13 (5-25)	27 (16-39)	.08
5 y	16 (7-28)	27 (16-39)	
NRM: pts with active disease received intervention			
2 y	8 (5-12)	26 (17-36)	<.001
5 y	9 (6-13)	31 (20-42)	
Grade 2 to 4 aGVHD after intervention, day +100			
All pts	20 (15-24)	37 (28-45)	.004
Pts in CR received intervention	22 (11-34)	27 (16-40)	.55
Any grade cGVHD (all patients), 1 y			
All pts	27 (22-33)	31 (22-39)	.50
Pts in CR received intervention	50 (34-64)	36 (22-50)	.11
Causes of death, all patients, No. (%)			
Relapse	179 (75.8)	64 (55.7)	<.001
Nonrelapse	57 (24.2)	51 (44.3)	

Abbreviations: aGVHD, acute graft-vs-host disease; allo-HCT1, first allogeneic hematopoietic cell transplant; allo-HCT2, second allogeneic HCT; cGVHD, chronic GVHD; CR, complete remission; DLI, donor lymphocyte infusion; LFS, leukemia-free survival; NRM, nonrelapse mortality; OS, overall survival.

[a] But NRM within 60 days of intervention.

[b] DLI (n = 121), allo-HCT2 (n = 46).

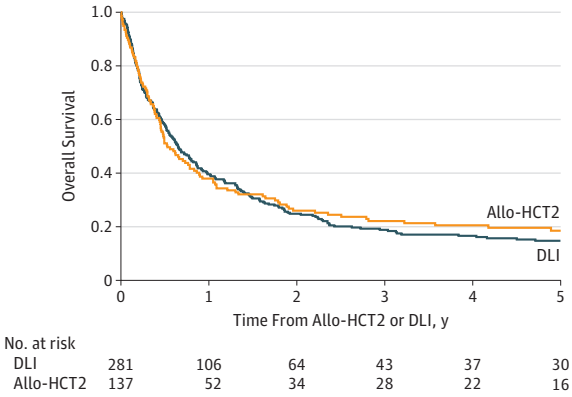
[c] DLI (n = 160), allo-HCT2 (n = 91).

18%-63%; *P* = .93), NRM (same, 22%; 95% CI, 9%-40% vs different, 28%; 95% CI, 9%-50%; *P* = .97), LFS (same, 26%; 95% CI, 9%-43% vs different, 18%; 95% CI, 0%-36%; *P* = .79) or relapse (same, 52%; 95% CI, 31%-69% vs different, 55%; 95% CI, 29%-75%; *P* = .99).

Patients Receiving Only Allo-HCT2 or DLI

Characteristics of patients treated with only allo-HCT2 or DLI are summarized in eTable 5 in the Supplement. At the time of intervention, allo-HCT2 patients were younger (median, 43 vs 50 years; *P* < .001), more likely to be in CR2/CR3

Figure 1. Overall Survival (OS) with a Second Allogeneic Hematopoietic Cell Transplant (Allo-HCT2) vs Donor Lymphocyte Infusion (DLI) in All Patients

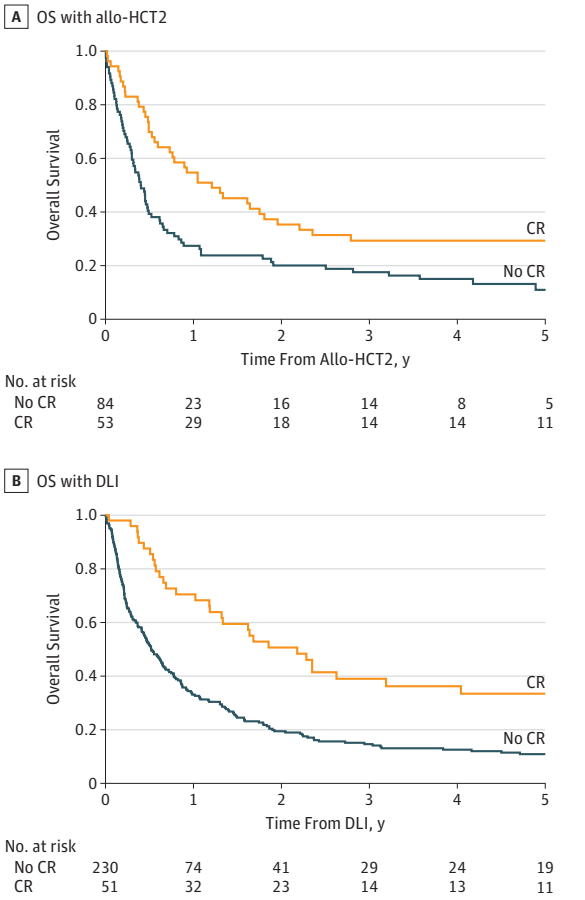


No. at risk

DLI	281	106	64	43	37	30
Allo-HCT2	137	52	34	28	22	16

Two-year OS for allo-HCT2, 26% (95% CI, 19%-33%) and DLI, 25% (95% CI, 20%-30%) (P = .86).

Figure 2. Overall Survival (OS) With a Second Allogeneic Hematopoietic Cell Transplant (Allo-HCT2) vs Donor Lymphocyte Infusion (DLI) in Patients With vs Without Complete Remission (CR)



No. at risk

No CR	84	23	16	14	8	5
CR	53	29	18	14	14	11

No. at risk

No CR	230	74	41	29	24	19
CR	51	32	23	14	13	11

A, Two-year OS with allo-HCT2 in patients with CR (35%; 95% CI, 22%-48%) vs no CR (active disease at the time of intervention) (20%; 95% CI, 11%-29%) (P = .002). B, OS with DLI in patients with CR (51%; 95% CI, 36%-65%) vs no CR (active disease at the time of intervention) (19%; 95% CI, 14%-25%) (P < .001).

(39.3% vs 20.4%; P < .001), had later relapse from an allo-HCT1 (median, 342 vs 193 days; P = .005), received intended therapy later (median, 68 vs 32 days; P < .0001), and had a higher incidence of prior grade 2 to 4 aGVHD (18% vs 8%; P = .003). Allo-HCT2 patients were less likely to receive cellular therapy from the same original donor (59.5% vs 100%; P < .001).

As reported in eTable 6 in the Supplement, a higher proportion of allo-HCT2 patients were in CR at the time of intervention and remained in CR afterward (39.3% vs 20.4%; P < .001), and a higher proportion who were not in CR at the time of intended intervention achieved CR afterward (38.5% vs 27.0%; P < .001). Nonrelapse mortality and grade 2 to 4 aGVHD were higher in allo-HCT2 recipients (eTable 6 in the Supplement). eTable 7 in the Supplement summarizes the causes of nonrelapse deaths.

Multivariable Analysis

Complete remission at the time of intervention (HR, 0.56; 95% CI, 0.42-0.76; P < .001), prior cGVHD (HR, 0.68; 95% CI, 0.50-0.93; P = .02), and longer time from allo-HCT1 to relapse (HR, 0.98; 95% CI, 0.98-0.99; P < .001) were associated with better OS. For NRM, allo-HCT2 vs DLI and prior grade 2 to 4 aGVHD resulted in a higher NRM (eTable 8 in the Supplement).

Discussion

To our knowledge, these results represent the largest study comparing outcomes of patients treated with either an allo-HCT2 or DLI after AML relapse of a prior allo-HCT1. Allo-HCT2 and DLI yielded comparable OS when patients were selected based on our current knowledge. Yet, OS was significantly better (HR, 0.55; 95% CI, 0.41-0.74; P < .001) if either one of the procedures was offered in CR (eTable 3 in the Supplement; Figure 2). Moreover, we identified that patients relapsing within less than 6 months from an allo-HCT1 have low OS, regardless of which intervention is offered (5-year OS: allo-HCT2, 9% vs DLI, 4%; P = .86) (Table 2). These findings are consistent with previously reported OS in patients receiving an allo-HCT2 for relapsed AML within less than 6 months from an allo-HCT1 and with active disease.[19] Also, the presence of poor-risk cytogenetics at the time of the original diagnosis remains associated with inferior OS after an allo-HCT2 or DLI.

When evaluating the incidence of grade 2 to 4 aGVHD, allo-HCT2 resulted in a nearly 2-fold higher incidence (37% vs 20%; P = .004). Allo-HCT2 was also an independent estimator for worse NRM (HR, 4.06; 95% CI, 2.32-7.08; P < .001). Conceptually, this inferior NRM may be explained by the additive toxic effects of chemotherapy or chemoradiotherapy regimens used for allo-HCT2 conditioning. Prior aGVHD negatively affected OS and NRM (eTables 3 and 4 in the Supplement). Although the exact mechanisms explaining the relationship between

prior aGVHD and worse NRM post allo-HCT2 or DLI are not clear, we believe that resulting organ damage from alloreactive donor cells predisposes to higher risk of death from procedure-related toxic effects. Accordingly, a thorough assessment of toxic effects associated with an allo-HCT1 is necessary to better help select patients to mitigate the risk of NRM. The presence of prior cGVHD did not adversely affect NRM; rather, it affected OS favorably when all patients were analyzed. This benefit was not the case when the analysis was restricted to patients in CR prior to intervention. We acknowledge that statistical power of the comparison could be impaired by the small numbers in the subgroup analysis. Several studies have reported a beneficial effect of cGVHD in reducing relapse rates after an allo-HCT1.[20-22] Yet, this benefit carries over after relapse of an allo-HCT during allo-HCT2 or DLI (eTables 3 and 8 in the Supplement). The retrospective nature of our study limits further investigation.

For patients who received intervention when in CR, using a donor other than a human leukocyte antigen-matched related donor resulted in worse NRM and inferior OS. This effect was limited to patients receiving allo-HCT2; use of unrelated donors, especially human leukocyte antigen mismatched, is associated with a higher risk of NRM in various studies.[23,24] No significant difference in OS between allo-HCT2 and DLI was observed when we restricted analysis to patients receiving only 1 of these treatments (eTable 8 in the Supplement).

Limitations

Our study has limitations. First, we could not determine the specific reasons why physicians favored an allo-HCT2 or DLI. Moreover, the nature of our study limits further analysis regarding a particular starting dose and/or schedule for DLI administration. Also, we could not evaluate the significance of donor chimerism (complete vs less than complete) as we did not have this information available immediately prior to intervention. Finally, our study was not designed to answer specific clinical scenarios such as the role of allo-HCT2 or DLI in AML relapsing in the central nervous system. These remain important research questions, to be studied prospectively

Conclusions

The heterogeneity of patient-, disease-, and treatment-related characteristics limits our ability to recommend one approach over another. Yet, OS appears to be comparable when offering allo-HCT2 or DLI after the first allograft-relapsed AML. Best results seem to be achieved in patients who relapse after 6 months from an allo-HCT1 or those who attain CR prior to an allo-HCT2 or DLI. In patients who relapse within less than 6 months or receive an intervention while having active disease, OS rates are low.

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Author Affiliations: Division of Hematology-Oncology, Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, Florida (Kharfan-Dabaja); Acute Leukemia Working Party, European Society for Blood and Marrow Transplantation, Paris Study Office, Paris, France (Labopin, Polge, Nagler, Mohty); Department of Blood and Marrow Transplantation and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, Florida (Nishihori); Section of Hematology-Oncology and Bone Marrow Transplantation Program, Department of Internal Medicine, American University of Beirut, Beirut, Lebanon (Bazarbachi); Department of Medicine, Hematology-Oncology, University of Freiburg, Freiburg, Germany (Finke); Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany (Stadler); Division of Hematology, Department of Internal Medicine, Dresden University Hospital, Dresden, Germany (Ehninger); Department of Hematology and Stem Cell Transplantation, University Hospital, Strasbourg, France (Lioure); Radboud University Medical Centre Nijmegen, Nijmegen, the Netherlands (Schaap); First State Pavlov Medical University of St. Petersburg Raisa Gorbacheva Memorial Research Institute for Paediatric Oncology, Hematology, and Transplantation, St Petersburg, Russia (Afanasyev); Hematology and BMT Department, Beilinson Hospital, Petach Tikva, Israel (Yeshurun); Department of Hematology, Umeå University Hospital, Umeå, Sweden (Isaksson); Department of Microbiology and Immunology, Laboratory of Clinical Bacteriology and Mycology, Catholic University Leuven, University Hospitals Leuven, Leuven, Belgium (Maertens); Division of Hematology, University of Geneva Hospitals and University of Geneva Medical School, Geneva, Switzerland (Chalandon); Section for Stem Cell Transplantation, Klinikum Augsburg, University of Munich, Munich, Germany (Schmid); Division of Hematology and Bone Marrow Transplantation, The Chaim Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel (Nagler); Hopital Saint-Antoine, Université Pierre and Marie Curie, Institut National de la Santé et de la Recherche Médicale Unite Mixte de Recherche U938, Paris, France (Mohty).

Author Contributions: Drs Kharfan-Dabaja and Labopin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Nagler and Mohty contributed equally to this study and share senior authorship.
Concept and design: Kharfan-Dabaja, Nishihori, Bazarbachi, Ehninger, Schmid, Nagler, Mohty.
Acquisition, analysis, or interpretation of data: Kharfan-Dabaja, Labopin, Polge, Nishihori, Bazarbachi, Finke, Stadler, Ehninger, Lioure, Schaap, Afanasyev, Yesherun, Isaksson, Maertens, Chalandon, Schmid.
Drafting of the manuscript: Kharfan-Dabaja, Polge, Nishihori, Mohty.
Critical revision of the manuscript for important intellectual content: Kharfan-Dabaja, Labopin, Nishihori, Bazarbachi, Finke, Stadler, Ehninger, Lioure, Schaap, Afanasyev, Yesherun, Isaksson, Maertens, Chalandon, Schmid, Nagler, Mohty.
Statistical analysis: Labopin, Nishihori.
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Supervision: Schaap, Yesherun, Nagler, Mohty.

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