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Survival of Patients with Acute Myeloid Leukemia Relapsing after Allogeneic Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research Study

Nelli Bejanyan [1,*], Daniel J. Weisdorf [1], Brent R. Logan [2,3], Hai-Lin Wang [2], Steven M. Devine [4], Marcos de Lima [5], Donald W. Bunjes [6], Mei-Jie Zhang [3]

[1] Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, Minnesota
[2] Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin
[3] Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin
[4] Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center – James, Columbus, Ohio
[5] Department of Medicine, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, Ohio
[6] Department of Internal Medicine III, Universitätsklinikum Ulm, Ulm, Germany

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A B S T R A C T

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 to 2010) during first or second complete remission (CR) to identify factors associated with longer postrelapse survival. Median time to post-HCT relapse was 7 months (range, 1 to 177). At relapse, 1231 patients (69%) received intensive therapy, including chemotherapy alone (n = 660), donor lymphocyte infusion (DLI) ± chemotherapy (n = 202), or second alloHCT ± chemotherapy ± DLI (n = 369), with subsequent CR rates of 29%. Median follow-up after relapse was 39 months (range, <1 to 193). Survival for all patients was 23% at 1 year after relapse; however, 3-year overall survival correlated with time from HCT to relapse (4% for relapse during the 1- to 6-month period, 12% during the 6-month to 2-year period, 26% during the 2- to 3-year period, and 38% for ≥3 years). In multivariable analysis, lower mortality was significantly associated with longer time from alloHCT to relapse (relative risk, .55 for 6 months to 2 years; relative risk, .39 for 2 to 3 years; and relative risk, .28 for ≥3 years; $P < .0001$) and a first HCT using reduced-intensity conditioning (relative risk, .77; 95% confidence interval [CI], .66 to .88; $P = .0002$). In contrast, inferior survival was associated with age >40 years (relative risk, 1.42; 95% CI, 1.24 to 1.64; $P < .0001$), active graft-versus-host disease at relapse (relative risk, 1.25; 95% CI, 1.13 to 1.39; $P < .0001$), adverse cytogenetics (relative risk, 1.37; 95% CI, 1.09 to 1.71; $P = .0062$), mismatched unrelated donor (relative risk, 1.61; 95% CI, 1.22 to 2.13; $P = .0008$), and use of cord blood for first HCT (relative risk, 1.23; 95% CI, 1.06 to 1.42; $P = .0078$). AML relapse after alloHCT predicted poor survival; however, patients who relapsed ≥6 months after their initial alloHCT had better survival and may benefit from intensive therapy, such as second alloHCT ± DLI.

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-transplantation 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 postrelapse survival and developing a risk stratification model.

A recent study by the European Blood and Marrow Transplantation group identified several prognostic factors associated with improved survival among AML patients who relapsed after reduced-intensity conditioning (RIC) alloHCT:

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* Correspondence and reprint requests: Nelli Bejanyan, MD, Division of Hematology, Oncology and Transplantation, 420 Delaware Street SE, Mayo Mail Code 480, Minneapolis, MN 55455.
E-mail address: nbejanya@umn.edu (N. Bejanyan).

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longer interval from transplantation 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 after 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 after alloHCT between 1990 and 2010. The CIBMTR is a research organization combined with the National Marrow Donor Program that collects information from over 500 transplantation centers worldwide that prospectively report detailed information on consecutive transplantations. To ensure data quality, a computerized system and scheduled data audits independently check all collected data based on specific disease forms provided by participating transplantation 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 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 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 or treatment-related 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 was 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 (nonproportional hazards), models were constructed breaking the post-transplantation time course into 2 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).

Table 1
Patient Characteristics

Variable	Total n (%)	Survival ≥1 Year after Relapse n (%)
No. 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)
0-18 yr	613 (34)	136 (33)
19-40 yr	439 (25)	138 (33)
41-76 yr	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-identical 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)
<6 mo	774 (43)	88 (21)
6 mo-2 yr	702 (39)	191 (46)
2-3 yr	138 (8)	52 (13)
≥3 yr	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 before relapse		
Yes	727 (41)	170 (41)
No	1028 (57)	234 (57)
Missing	33 (2)	9 (2)
Treatment for relapse		
Second 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, mo	39 (<1-193)	59 (12-193)

ATG indicates antithymocyte globulin; CSA, cyclosporine; tac, tacrolimus.

RESULTS

Patient Characteristics

We identified 1788 patients with AML relapsing after alloHCT from 286 CIBMTR centers in 43 countries. Of these, 413 patients survived ≥1 year after relapse (Table 1). Median