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Isolated Extramedullary Relapse as a Poor Predictor of Survival after Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia

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A B S T R A C T

Limited and conflicting data exist on outcomes of patients with extramedullary relapses (EMRs) after allogeneic hematopoietic cell transplantation (allo-HCT) for acute leukemias. We retrospectively reviewed charts of consecutive allo-HCT recipients who underwent transplantation in our center with the indication of acute leukemia (July 1990 to July 2018). Incidences of isolated EMR (iEMR) and bone marrow relapse (BMR) were calculated using cumulative incidence (CI) analysis, with each and treatment-related mortality considered a competing risk. We studied 554 allo-HCT recipients for 1.8 years (range, .04 to 27.75). Ten-year CI of 10.5% for iEMR was associated only with advanced disease phase at transplantation, whereas 10-year CI of 34.8% for BMR was independently associated with pretransplant disease phase, lines of treatment, and fungal infections. Most iEMR and BMR patients (75% and 81%, respectively) received systemic treatment combined with local radiation for iEMR (26%) and donor lymphocyte infusions (16% and 28%, respectively) when feasible. Extensive chronic graft-versus-host disease (GVHD) was recorded in 47% of iEMR and 48% of BMR patients. Outcomes were poor both in iEMR (10-year overall survival [OS], 18.3%) and BMR (10-year OS, 19.1%). Independent predictors of OS were disease phase, type of donor, acute and chronic GVHD, fungal infections, iEMR, and BMR. In a large population with long-term follow-up, incidence of iEMR was relatively high, developed at the late post-transplant period, and was associated only with disease phase at transplantation. Furthermore, iEMR and BMR conferred similarly poor outcomes despite systemic treatment or extensive chronic GVHD.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) represents the only potentially curative option for patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) [1]. However, relapse of the underlying disease remains the leading cause of death for allo-HCT recipients [2]. Despite advances in transplant modalities and novel targeted treatments over the last decades, prognosis of relapsed patients after allo-HCT remains poor. The key therapeutic advantage of allo-HCT against relapse has been the graft-versus-leukemia (GVL) effect that is augmented by therapeutic modulations in relapsed patients after allo-HCT. In patients with extramedullary relapse (EMR), however, the GVL effect is ineffective, suggesting that leukemic cells may escape the GVL effect in sanctuary sites [3].

EMR has traditionally been considered relatively uncommon after allo-HCT, varying from .65% to 20% of patients [4–6]. However, older studies have included heterogeneous patient populations with differences in disease phases and transplantation modalities applied over the years. Recent data on EMR have also provided conflicting results on the role of underlying disease, extramedullary involvement, and GVL effect. A few studies showed a significantly higher incidence of EMR in ALL compared with AML [7–10], whereas Gunes et al. [8] also reported that chronic graft-versus-host-disease (GVHD)

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decreased the risk of EMR. Other studies did not confirm these findings [9,11,12] but highlighted extramedullary disease before HCT as a significant predictor of relapse [9,11].

Given the diversity of recent data on EMR after allo-HCT, we aimed to retrospectively investigate EMR in our large cohort of allo-HCT recipients with long-term follow-up. The primary endpoint was the incidence of isolated EMR (iEMR) after HCT and its impact on outcomes (overall survival [OS] and treatment-related mortality) as compared with patients with bone marrow relapse (BMR) and those without relapse. Secondary endpoints were identifying risk factors associated with EMR and current treatment options.

METHODS

Patient Population

We enrolled consecutive allo-HCT recipients transplanted with the indication of acute leukemia in our Joint Accreditation Committee ISCT-Europe & European Society for Blood and Marrow Transplantation accredited unit (July 1990 to July 2018). We retrospectively extracted patient data including details of the transplant procedure, disease status, response rates, toxicity, survival time, and time to progression from our prospectively acquired database. All charts from patients with EMR were re-reviewed to record detailed data regarding timing, diagnosis, and treatment of relapse. Our institutional review board and ethics committee of G. Papanicolaou Hospital approved this study. All patients gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Transplantation Procedures

Patients underwent allo-HCT according to the standard European Society for Blood and Marrow Transplantation indications and standard operating procedures of our unit. Briefly, the most common myeloablative conditioning regimens were either busulfan/cyclophosphamide or total body irradiation (TBI)/cyclophosphamide. Busulfan/cyclophosphamide consisted of p.o. busulfan 4 mg/kg/day for 4 days for a total dose 16 mg/kg or i.v. busulfan formulation 3.2 mg/kg/day for 4 days (ie, .8 mg/kg per dose infused i.v. over 2 hours, every 6 hours for 4 days), and cyclophosphamide 60 mg/kg/day for 2 days. The radiation containing regimen was composed of fractionated TBI followed by cyclophosphamide (total dose, 120 mg/kg). TBI was administered in 6 fractions of 240 Gy twice a day over 3 days to a total dose of 1440 cGy.

All patients had protective lung shielding. Customized lung blocks were used to reduce the lung dose to 12 Gy, as previously described [13]. Haploidentical transplantees received either ex vivo T cell–depleted grafts or post-transplant cyclophosphamide (total dose, 100 mg/kg). Patients ineligible for conventional allo-HCT received a reduced-intensity or -toxicity conditioning regimen consisting of fludarabine (30 mg/kg/day for 5 days, total dose of 150 mg/kg) plus busulfan (4 mg/kg/day for 2 days, total dose of 8 mg/kg), or treosulfan (14 g/m^2/day for 3 days), as previously described [14]. Antithymocyte globulin (2.5 to 10 mg/kg) was administered as part of the conditioning in unrelated and alternative transplantations, as previously described [15].

Acute and chronic GVHD were assessed and graded according to established criteria [16,17]. In the present analysis, acute GVHD grade $\geq$ II and extensive chronic GVHD were reported as clinically relevant. The most widely used prophylactic regimen for GVHD was a combination of a calcineurin inhibitor (cyclosporine or tacrolimus) in the short term, 4 doses of post-transplant methotrexate for those patients who received myeloablative regimens, and cyclosporine plus mycophenolate mofetil for those patients who received reduced-intensity conditioning regimens. Cyclosporine, tacrolimus, and creatinine serum levels were monitored after allo-HCT, and dose adjustments were made appropriately. In the absence of active GVHD, cyclosporine was discontinued within 3 to 6 months of sibling allo-HCT and tacrolimus within 9 to 12 months in unrelated allo-HCT. Treatment of chronic GVHD consisted of methylprednisolone and readministration of cyclosporine, if already withdrawn. In steroid-resistant GVHD, several combinations of immunosuppressive drugs and extracorporeal photopheresis were used as subsequent lines of treatment [18].

Infection prophylaxis consisted of acyclovir for viral infections and trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* infection. Low dose of liposomal amphotericin B or voriconazole or caspofungin was given for prophylaxis or in case of aspergillosis history. Preemptive antiviral treatment with ganciclovir, foscarnet, or valganciclovir was administered for patients with cytomegalovirus reactivation detected by a molecular method. Severe infections requiring systemic therapy and hospitalizations were documented in our records.

Assessment of EMR

All patients with signs or symptoms of relapse were evaluated by physical examination, imaging, bone marrow assessment, biopsy of the involved tissue when possible, and cerebrospinal fluid testing where indicated. Patients were treated with either systemic or local therapies. Systemic treatment was divided into intensive or palliative treatment. Intensive treatment included chemotherapeutic regimens causing profound cytopenia, donor lymphocyte infusions with or without targeted therapies (ie, tyrosine kinase inhibitors in Philadelphia positive patients), radiation, or hypomethylating agents for AML. Patients with central nervous system (CNS) involvement confirmed by cerebrospinal fluid or imaging studies received additional intrathecal chemotherapy.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY). Continuous variables were described as median and range and categorical variables as frequencies. Patient-, disease-, and transplant-related variables were compared using chi-square statistics for categorical variables and the Kruskal-Wallis test for continuous variables. Patients were classified as having early disease at transplantation when they were transplanted in first complete remission, whereas patients transplanted in late or undefined complete remission were classified as advanced disease at transplantation. Lines of treatment were calculated based on the lines of chemotherapy or radiotherapy the patient received before transplant. Patients with BMR who also presented EMR were classified into the BMR group. Incidence of iEMR was calculated using cumulative incidence (CI) analysis, with iEMR, BMR, and treatment-related mortality considered a competing risk using EZR software (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html) [19].

Statistical significance was assessed by the Gray test and Fine and Gray regression modeling. Kaplan-Meier estimates were used to calculate the probability of OS. Multivariate analysis was performed using Cox proportional hazards model for OS. Subgroup analyses were performed according to disease (AML or ALL), site of relapse (CNS versus other sites), and period of transplant (early for patients transplanted between 1990 and 2004 and late for patients transplanted between 2005 and 2018). Level of statistical significance was defined at .05.

RESULTS

Patient Population

Among 554 allo-HCT recipients followed for 1.8 years (range, .04 to 27.75), 61 patients (11%) presented with EMR. Most EMRs involved the CNS (56%). Other sites of EMR included skin (11 patients), testes (5), joints (3), breast (1), lungs (1), kidneys (1), peritoneum (1), spleen (1), stomach (1), bones (1), and amygdala (1). Patient characteristics are shown in Table 1. Among the 3 groups (iEMR, BMR, and no relapse), there was significant difference in gender (P = .017), disease phase at transplantation (P < .001), type of donor (P = .012) and severe acute GVHD (grades II to IV, P = .009).

Incidence of iEMR versus BMR

Isolated EMR was observed in 38 patients (6.8%) at a median of 9.5 post-transplant months (range, 1.8 to 67.3). CI of iEMR was 7.8% at 2 years, 9.7% at 5 years, and 10.5% at 10 years. iEMR CI was associated only with advanced disease phase at transplantation (P < .001). The presence of extramedullary disease pretransplant was not associated with iEMR incidence. BMR was observed in 149 patients (26.9%) at a median of 9 months (range, .3 to 276). CI of BMR was 26.9% at 2 years, 30.6% at 5 years, and 34.8% at 10 years. In the multivariate analysis, BMR CI was independently associated with pretransplant disease phase (P < .001), lines of treatment (P = .042), and fungal infections (P < .001).

Outcomes of iEMR versus BMR

Most iEMR and BMR patients (75% and 81%, respectively) received systemic treatment (intensive chemotherapy or hypomethylating agents for AML since 2008) combined with local radiation for iEMR (26%) and donor lymphocyte infusions (16% and 28%, respectively) when feasible. Second HCT was performed in a limited number of patients with BMR, using the original donor (9 patients, 6%). Extensive chronic GVHD was recorded in 47% of iEMR and 48% of BMR patients. In most patients (87% of iEMR and 79% of BMR), GVHD occurred after

Table 1
Patient Population Characteristics According to Relapse Groups

	iEMR (n = 38)	BMR (n = 149)	No relapse (n = 367)	*P*
Median age, yr (range)	34 (13-61)	36 (4-66)	36 (8-69)	.461
Male gender	17 (45)	41 (27)	157 (43)	.017
Diagnosis				
AML	18 (47)	90 (60)	188 (51)	.171
ALL	20 (53)	59 (40)	79 (49)	
Phase at transplant				
First complete remission	12 (32)	46 (30)	239 (65)	<.001
Other complete remission	9 (24)	42 (23)	80 (22)	
Relapsed/refractory	17 (44)	61 (47)	48 (13)	
Myeloablative conditioning	29 (76)	104 (69)	263 (71)	.345
TBI-based conditioning	11 (29)	36 (24)	110 (30)	.340
Donor type				
Sibling	25 (66)	103 (69)	207 (56)	.012
Unrelated	12 (36)	37 (25)	141 (38)	
Alternative	1 (3)	9 (6)	19 (5)	
Severe acute GVHD	5 (13)	27 (18.5)	93 (26.5)	.009
Extensive chronic GVHD	18 (47)	71 (48)	190 (52)	.403

Values are n (%) unless otherwise defined.

therapeutic modulations. Ten-year treatment-related mortality of our entire cohort was 33.2%. Treatment-related mortality could not be calculated in patients with iEMR or BMR because it was considered a competing event. Deaths associated with treatment of relapse were observed in 22% of patients receiving systemic treatment.

Outcomes were poor in iEMR patients, with a 10-year OS of 18.3%. Favorable OS in iEMR patients was associated only with sibling donors ($P = .049$) but not with other factors, such as treatment with donor lymphocyte infusions or presence of chronic GVHD. Similarly, poor outcomes (10-year OS of 19.1%) were observed in BMR patients. In the multivariate model, favorable OS was independently associated only with the diagnosis of AML ($P = .050$) and absence of bacterial infections ($P = .049$).

Figure 1 presents Kaplan-Meier curves of OS for patients with relapse (A, $P < .001$) and patients with iEMR or BMR (B, $P < .001$) compared with nonrelapsed patients. Independent predictors of OS in the entire cohort were disease phase at transplantation ($P = .039$), type of donor ($P < .001$), acute ($P = .014$) and chronic GVHD ($P = .021$), fungal infections ($P < .001$), iEMR ($P = .024$), and BMR ($P = .001$), as shown in the multivariate model (Table 2).

Subgroup Analyses of Patients with EMR

We further performed subgroup analyses of patients with EMR according to disease (AML versus ALL), site of relapse (CNS versus other sites), and period of transplant (early versus late). Regarding disease, patients with ALL had a significantly higher rate of CNS involvement (75% versus 46%, $P = .034$), lower rate of BMR (15% versus 49%, $P = .023$), higher rate of TBI-based conditioning (60% versus 5%, $P < .001$), and younger age (29 ± 12 versus 40 ± 15 years, $P = .014$) compared with AML patients. Regarding site of relapse, patients with CNS relapse presented with higher rates of ALL (44% versus 19%, $P = .034$). Regarding the treatment period, patients transplanted in the early period showed higher rates of AML (82% versus 50%, $P = .035$) and higher rates of extramedullary disease at diagnosis (65% versus 26%, $P = .008$). Nevertheless, no significant differences were observed in outcomes (acute or chronic GVHD and OS) among the studied subgroups (disease, site of relapse, or treatment period).

DISCUSSION

In our large population with long-term follow-up, incidence of iEMR was relatively high, developed mostly in the CNS during the late post-transplant period, and was associated only with disease phase at transplantation. More importantly, iEMR conferred similarly poor outcomes compared with BMR, despite therapeutic modulations and the development of chronic GVHD.

Indeed, CNS seems to be the most common extramedullary involvement site in most clinical studies in ALL patients [7]. Regarding risk factors for EMR, studies of AML patients reported that extramedullary involvement before transplantation had no impact on outcome [20,21], similar to our large study in both AML and ALL. Despite the reportedly higher incidence of EMR in ALL compared with AML [7–10], our study did not confirm this finding. Other studies also suggested that busulfan-based conditioning may be associated with higher risk for EMR than TBI-based [8,22]. However, our study and a previous study in a large cohort have not confirmed these findings [9].

Gunes et al. [8] also reported that chronic GVHD decreases the risk of EMR. Large studies, like ours, did not confirm these findings [9,11,12]. Although the GVL effect has been associated with GVHD and can reduce BMR after allo-HCT [3], available evidence suggests that it has a lower impact on iEMR. In an analysis of acute GVHD effects on BMR versus iEMR, acute GVHD was associated only with lower BMR and not iEMR [6]. In our study, extensive chronic GVHD developed mostly after therapeutic modulations. Nevertheless, GVHD development did not lead to better outcomes for our relapsed patients. These data support the theory of an ineffective GVL effect in extramedullary sites, probably due to inadequate immunologic surveillance of the graft.

In some studies, it was reported that iEMR had a better prognosis than BMR [9,12]. Unlike this finding, OS in these 2 groups was similar in our study despite high rates of systemic intensified treatment. There is no established standard of care treatment for EMR. Our practice is to treat EMR systemically in combination with local control of disease when indicated, followed by cellular therapy (donor lymphocyte infusions or second transplantation). Solh et al. [12] found that the type of treatment (local, systemic, or combined) and the response to treatment were significantly associated with survival after EMR. Immune therapy was important for treatment success.

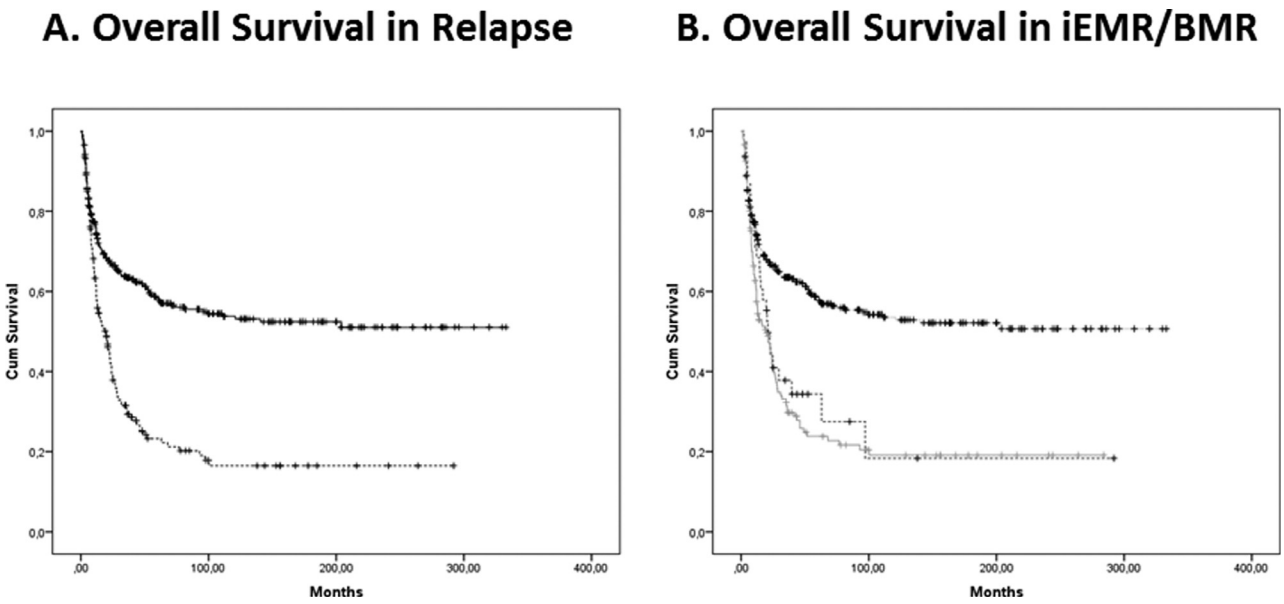

Figure 1. (A) Decreased OS in patients with relapse (*dotted line*) compared with nonrelapsed patients ($P < .001$) (B) Decreased OS in patients iEMR (*dotted line*) or patients with BMR (*gray line*) compared with nonrelapsed patients ($P < .001$).

Table 2
Multivariate Model of OS Predictors

	Exp(B)	*P*	Lower 95% Confidence Interval	Upper 95% Confidence Interval
Disease phase	1.219	.039	1.011	1.470
Donor type (sibling/unrelated/alternative)	1.877	<.001	1.404	2.511
Fungal infections	.511	<.001	.353	.739
BMR	.547	.001	.387	.773
Acute GVHD	.645	.014	.455	.915
Chronic GVHD	1.444	.021	1.056	1.974
iEMR	.569	.024	.348	.930
Bacterial infections	.780	.124	.568	1.071
Viral infections	.910	.559	.664	1.248
HLA matched donors	.973	.885	.688	1.417

In the era of novel biologic, immune and cellular therapies, the natural course of EMR after allo-HCT is expected to change dramatically. A few case reports have suggested hints of these expectations with blinatumomab reported to induce discordant CD19 expression between bone marrow and extramedullary sites [23]. Another report showed a GVL effect of blinatumomab in relapsed ALL patients after allo-HCT [24]. More importantly, beneficial effects of chimeric antigen receptor T cell therapy have been also reported in an ALL patient with EMR after allo-HCT [25]. The role of immune therapy has also been recently strengthened by the experience with novel immune therapies that were introduced into the treatment of advanced hematologic malignancies. In particular, ipilimumab, an immune checkpoint blocking agent targeting cytotoxic T lymphocyte–associated protein 4, has been explored in the treatment of post-transplant relapse. This agent was shown to restore antileukemia effects of donor T cells, and promising initial results have been observed in EMR of AML [26].

Our study has some limitations. First, because of its retrospective nature, results should be interpreted with caution. Second, it represents a single-center experience over a long period of time during which advances in diagnostics and therapeutics along with accumulated clinical experience of treating physicians may have led to improved outcomes. However, no difference in outcomes was found between the early and late time period in the subgroup analysis. Furthermore, this study was conducted according to standard operating procedures in a large patient population with a long-term follow-up, adding significant data to the existing literature on EMR.

In conclusion, iEMR is emerging as an important type of relapse after allo-HCT, with poor outcomes, comparable with that of BMR. Increased awareness among treating physicians is needed in an effort to prevent relapse and achieve longer survival. In the era of novel biologic, immune, and more sophisticated cellular therapies, the natural course of EMR after allo-HCT is expected to change dramatically.

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Authorship statement: I.S., I.B., D.M., and A.A. were responsible for study conception and design. C.A., M.I., G.V., Z.B., and C. L. recruited study participants. M.G., S.B., and M.M. collected clinical data. E.G., E.Y., M.P., K.C., and S.P. analyzed and interpreted the data. I.S., E.G., and A.A. drafted the manuscript and performed critical revisions. All authors approved the final version of the manuscript.

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