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Outcomes of Adults with Acute Lymphoblastic Leukemia Relapsing after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

For patients with acute lymphoblastic leukemia (ALL) who relapse after allogeneic hematopoietic stem cell transplantation (HSCT), treatment options are limited, and the clinical course and prognostic factors affecting outcome have not been well characterized. We retrospectively analyzed outcomes of 123 adult patients with ALL who relapsed after a first HSCT performed at our center between 1993 and 2011. First-line salvage included second HSCT (n = 19), donor lymphocyte infusion with or without prior chemotherapy (n = 11), radiation therapy (n = 6), cytoreductive chemotherapy (n = 30), mild chemotherapy (n = 27), or palliative care (n = 23), with median postrelapse overall survival (OS) of 10 months, 6.5 months, 3 months, 4 months, 4 months, and 1 month, respectively. Despite a complete remission rate of 38% after first-line salvage in the treated patients, the OS rate remained limited with 1- and 2- year OS rates of 17% (95% confidence interval, 13 to 29) and 10% (95% confidence interval, 6 to 20), respectively. On univariate analysis, adverse factors for OS included active disease at the time of first HSCT and short time to progression from first HSCT (<6 months). There was no difference in the 6-month survival postrelapse in patients with isolated extramedullary relapse (44%) compared with combined extramedullary and bone marrow relapse (29%) or those with isolated bone marrow relapse (34%) ($P = .8$). Our data provide more insight into the disease behavior and treatment outcomes of ALL at relapse after HSCT against which future trials may be compared.

INTRODUCTION

Treatment outcomes for adults with acute lymphoblastic leukemia (ALL) have improved during the last few decades. Measures such as optimized chemotherapy regimens, modeled after pediatric regimens [1,2]; risk stratification with minimal residual disease monitoring [3,4], development of novel agents [5,6], and improvements in supportive care have led to improvement in survival rates. Results from a number of trials, including the pivotal MRC/UKALL XII/ECOG E2993 trial, have led to more interest in the up front use of allogeneic hematopoietic stem cell transplantation (HSCT) for both standard-risk and high-risk ALL patients [7,8].

Patients with ALL who relapse after HSCT have a poor prognosis. Some patients do respond to subsequent treatment, and prognostic factors for these patients are not well characterized. Few studies have evaluated management of ALL relapse after HSCT. Spyridonidis et al. [9] reviewed the registry data from the European Blood and Marrow Transplantation (EBMT) group and demonstrated a median postrelapse survival of only 5.5 months and an estimated 5-year postrelapse survival of 8% ± 1%. Using a multivariate model, the authors reported a prognostic model at the time of relapse.

The nature of a retrospective registry study, however, precludes a more in-depth look at specific patient populations within the group, such as patients with extramedullary (EM) relapse. In addition, limited data are available on factors such as discontinuation of immunosuppressive therapy (IST), as well as more details on salvage therapy and its responses, and the impact of these factors on the outcomes of the patients. Examinations of these issues are warranted to guide postrelapse management decisions and to explore novel therapeutic interventions. We performed a single-center retrospective analysis on adults with hematological relapse after first HSCT for ALL in an attempt to better characterize these issues.

METHODS

Patient Inclusion Criteria and Data Collection

This retrospective analysis included all adult ALL patients, age 18 years or older, who had undergone first HSCT at M.D. Anderson Cancer Center between 1993 and 2011 and subsequently relapsed. Patients were treated on transplantation protocols that were available during the different time periods. Collected data included patient and disease characteristics at diagnosis, disease status at time of first HSCT, source of stem cells, allotype of donor, conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, incidence of acute and chronic GVHD after transplantation, duration of posttransplantation remission, leukemia burden at relapse, details of salvage therapy and outcome variables, including response, overall survival (OS), and cause of death. Institutional review board approval was obtained for this retrospective study.

Definitions

Cytogenetic abnormalities were classified based on previously published reports [10]. Myeloablative and reduced-intensity conditioning regimens were defined according to the Center for International Blood and Marrow Transplantation Research criteria [11]. Criteria for complete response (CR) included normal cytogenetics, the absence of circulating blasts, and less than 5% marrow blasts. The disease stage at transplantation

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Table 1
Overall Characteristics of Relapsed Patients by Salvage Treatment Group

Characteristic	Overall (n = 123)	HD Chemotherapy (n = 30)	HSCT ± Chemotherapy (n = 19)	DLI ± Chemotherapy (n = 11)	Gentle Chemotherapy (n = 27)	Radiation or IT only (n = 6)	Palliative (n = 23)
Median age, yr (range)	31 (18-70)	38 (21-64)	31 (19-51)	35 (23-53)	27 (18-70)	34 (22-42)	29 (18-68)
Response pretransplantation							
Disease in remission	83 (67%)	25 (83%)	15 (79%)	5 (45%)	19 (70%)	3 (50%)	11 (48%)
Active disease	40 (33%)	5 (17%)	4 (21%)	6 (55%)	8 (30%)	3 (50%)	12 (52%)
Histology							
B lineage	95 (77%)	23 (77%)	17 (89%)	8 (73%)	22 (81%)	3 (50%)	16 (70%)
T lineage	28 (23%)	7 (23%)	2 (11%)	3 (27%)	5 (19%)	3 (50%)	7 (30%)
Cytogenetic risk category*							
High risk	46 (37%)	13 (43%)	9 (47%)	5 (45%)	10 (37%)	1 (17%)	7 (30%)
Others	53 (43%)	12 (40%)	9 (47%)	3 (27%)	12 (44%)	1 (0%)	12 (52%)
Unknown	24 (20%)	5 (17%)	0 (0%)	4 (36%)	5 (19%)	4 (67%)	4 (17%)
Site of relapse							
Systemic relapse	99 (80%)	23 (77%)	17 (89%)	10 (91%)	23 (85%)	0 (0%)	19 (83%)
Isolated EM†	24 (20%)	7 (23%)	2 (11%)	1 (9%)	4 (15%)	6 (100%)	4 (17%)
Preparative regimen							
Myeloablative	91 (74%)	24 (80%)	16 (84%)	8 (73%)	17 (63%)	4 (67%)	16 (70%)
RIC	32 (26%)	6 (20%)	3 (16%)	3 (27%)	10 (37%)	2 (33%)	7 (30%)
Allo type							
Matched unrelated donor	45 (37%)	9 (30%)	4 (21%)	7 (64%)	9 (33%)	1 (17%)	12 (52%)
Matched related donor	65 (53%)	16 (53%)	14 (74%)	4 (36%)	15 (56%)	5 (83%)	7 (30%)
Mismatched related	6 (5%)	4 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (9%)
Umbilical cord blood	7 (6%)	1 (3%)	1 (5%)	0 (0%)	3 (11%)	0 (0%)	2 (9%)
Time from HSCT to progression							
≤6 mo	81 (66%)	15 (50%)	7 (37%)	7 (64%)	22 (81%)	4 (67%)	21 (91%)
≥6 mo	42 (34%)	15 (50%)	12 (63%)	4 (36%)	5 (19%)	2 (33%)	2 (9%)
PB blasts at relapse							
≤10%	96 (78%)	24 (80%)	13 (68%)	10 (91%)	21 (78%)	6 (100%)	18 (78%)
≥10%	27 (22%)	6 (20%)	6 (32%)	1 (9%)	6 (22%)	0 (0%)	5 (22%)
EBMT score‡	(n = 83)	(n = 25)	(n = 15)	(n = 5)	(n = 19)	(n = 3)	(n = 11)
Score 0-1	43 (52%)	18 (72%)	10 (67%)	4 (80%)	7 (37%)	1 (33%)	2 (18%)
Score 2-3	40 (48%)	7 (28%)	5 (33%)	1 (20%)	12 (63%)	2 (67%)	9 (82%)

HD indicates high dose; IT, intrathecal; RIC, reduced-intensity conditioning; PB, peripheral blood.
Overall survival was calculated from the time of progression.

* Cytogenetic risk category based on National Comprehensive Cancer Network (NCCN) guidelines 2012 [10].

† Locations were CNS (n = 16), lymph node (n = 5), joints (n = 2), testes (n = 1), and others (n = 5). Five patients had more than 1 site of extramedullary relapse.

‡ Based on study by Spyridonidis et al. [9]. Applied to patients in study who underwent HSCT while in remission.

was defined using established criteria. Response was documented as the best response occurring after day 30 after HSCT. Hematological relapse was defined by recurrence of blasts in the peripheral blood or infiltration of the bone marrow (BM) by more than 5% blasts. Isolated EM relapse had to be proven with biopsy.

IST was defined as being continued if not discontinued after relapse until time of last follow-up or death or if patients died within 2 weeks of stopping IST. Treatment regimens used for control of the leukemia after relapse were defined as intensive if a combination of cytotoxic agents was used. Mild therapy was defined as combinations of steroids and vincristine;

Table 2
Response and Outcomes to Salvage Treatment

Treatment	N = 93 (%)	CR Rates (%)	Median OS (mo)	Number, Cause of Death
Mild therapy	27 (29)	41	4	TRM (n = 1)
Single-agent chemotherapy (n = 6): (clofarabine, n = 2; nelarabine, n = 2; azacitidine, n = 1; hydrea, n = 1)				Disease relapse (n = 25)
Novel therapeutic agents/ trial medications (n = 13)				
Steroids/gentle chemotherapy (n = 2)				
TKIs (n = 6)				
Intensive chemotherapy	30 (32)	27	4	TRM (n = 2)
MTX /Ara C (n = 4)				Disease relapse (n = 24)
HyperCVAD/augmented HyperCVAD [24] (n = 20)				Unknown (n = 1)
MOAD [25] (n = 4)				
Others (n = 2)				
Radiotherapy or IT alone	6 (7)	83	3	TRM (n = 1)
				Disease relapse(n = 4)
DLI	11 (12)	64	6.5	TRM (n = 2)
+ Intensive chemotherapy (n = 8)				Disease relapse (n = 9)
+ Mild chemotherapy (n = 3)				
Second HSCT	19 (20)	84	10	TRM (n = 5)
+ Intensive chemotherapy (n = 14)				Disease relapse (n = 8)
+ Mild chemotherapy (n = 5)				

TRM indicates treatment-related mortality; MTX, methotrexate; Ara-C, cytarabine; IT, intrathecal; HyperCVAD, fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone combined with methotrexate, cytarabine; MOAD, methotrexate, vincristine, L-asparaginase, and dexamethasone.

use of a single cytotoxic drug such as clofarabine, nelarabine, vincristine, or hydroxyurea; use of targeted therapies such as NOTCH inhibitors or tyrosine kinase inhibitors (TKI); or use of immunomodulatory agents such as antibodies or hypomethylating agents. Donor lymphocyte infusion (DLI) was defined as the infusion of unstimulated lymphocytes collected from the original donor. Acute GVHD was clinically graded as 0 to IV based on standard criteria [12,13], and chronic GVHD was classified as none, limited, or extensive as described previously [14].

Statistical Analysis

The primary outcome of interest was survival after relapse following HSCT. Actuarial OS was estimated by the method of Kaplan-Meier. Survival according to patients' characteristics was compared using Cox's proportional hazards regression analysis. Comparison was limited to univariate analysis because of sample size limitation and the heterogeneity of the salvage therapy after relapse. Continuous variables were compared using the Wilcoxon rank-sum test. Statistical significance was defined at the .05 level. Analysis was performed using STATA.11 (StataCorp LP, College Station, TX).

RESULTS

Patient, Disease, and Relapse Characteristics

Between 1993 and 2011, 381 adults with ALL underwent HSCT at M.D. Anderson Cancer Center, and 123 (32%) subsequently relapsed. The patient characteristics are summarized by the salvage treatment they received at time of relapse in Table 1. For the whole group, the median age at diagnosis was 31 years (range, 18 to 70 years, with 4 patients older than 60 years). A significant proportion of patients had high-risk features, including 37% (n = 46) with high-risk cytogenetics (including 23% who were Ph+). In addition, 78% of patients (n = 95) were that underwent tranplantation beyond CR1, with 33% (n = 40) that underwent tranplantation with active disease. Most patients received a myeloablative conditioning regimen (74%, n = 91).

Patients were that underwent tranplantation from a sibling donor in 53% of cases (n = 65), matched unrelated donor in 37% (n = 45), mismatched related donor in 5% (n = 6), and from a cord blood source in 6% (n = 7). The source of stem cells was peripheral blood for most patients (n = 74). The median time from transplantation to relapse was 4 months (range, 1 to 38 months). At the time of relapse, 80% of patients (n = 99) had systemic relapse, whereas 20% (n = 24) had isolated extramedullary relapse (Table 1).

Management of Relapse, Response, and Overall Survival

At the time of relapse, 23 patients received only supportive care, whereas data on the treatment of 7 others were limited because they were treated at other hospitals after relapse. The remaining 93 patients received some form of antileukemic therapy as described in Table 2. The choice of initial salvage treatment was at the discretion of the attending physician and patient and consisted of chemotherapy alone (mild, 22%; intensive, 24%), radiation therapy/intrathecal therapy alone (5%), DLI ± chemotherapy (9%), and HSCT ± chemotherapy (15%). Of note, most patients who received mild chemotherapeutic agents, including targeted or immunomodulatory agents, were those that underwent tranplantation after 2000. Among the Ph-positive patients (n = 28), 20 received TKIs (±chemotherapy) as part of their salvage therapy. Imatinib, a first-generation TKI, was used in relapses between 2001 and 2005 (n = 9), whereas in most relapses from 2006 onward, second-generation (dasatinib or nilotinib) or third-generation (ponatinib) TKIs were used for first-line or subsequent salvage chemotherapy (n = 11).

The decision to proceed to second transplantation was at the discretion of the treating physician and involved patient. Patients who received second transplantations were more likely to be in CR (n = 14/19) and had a relatively prolonged duration of remission (>6 months) with their first transplantation (n = 12/19) (Table 1). Donors for second HSCT were changed in 47% of cases (n = 9/19). Outcomes and prognostic factors for second transplantations were reported previously [15].

Overall, 38% of all patients achieved CR after their first-line salvage. With a median follow-up among surviving patients of 11 months (range, 1 to 107 months), the median OS rate in all patients was 4 months. The 1- and 2-year OS rate for all patients was 17% (95% confidence interval [CI], 13 to 29) and 1 % (95% CI, 6 to 20), respectively.

The median survival by treatment group was 10 months in the second HSCT group; 6.5 months in the DLI group; 4 months in the chemotherapy-only group, with no difference in survival whether intensive or mild chemotherapy was administered; and 3 months in the radiation therapy or intrathecal therapy group (Table 2). For patients who received palliation only, the median survival was 1 month.

Disease status at time of first transplantation and time to relapse after first transplantation were found to be significant predictors for worse survival in univariate analysis (Table 3). Patient age, cytogenetic risk, and immunophenotype did not have a significant impact on OS. Figure 1 shows the OS rates among the patients who relapsed within 6 months after HSCT compared with those who relapsed later.

Treatment and Outcomes of Patients with Extramedullary Relapse

At the time of relapse, 85 patients had isolated BM relapse, whereas 38 had relapse in EM sites, either isolated (n = 24) or with concurrent BM relapse (n = 14) (Table 1).

Table 3
Univariate Analysis of Factors Influencing 6-Month OS after Relapse

Covariates	N (123)	Hazard Ratio	95% CI	*P*
Age at HSCT, yr				
≤30	55	Ref.		
>30	68	.7	.5-1.1	.2
Sex				
Female	39	Ref.		
Male	84	1.7	1.01-2.8	.05
Lineage				
B cell	95	Ref.		
T cell	28	1	.6-1.7	.99
Cytogenetic				
Ph−	71	Ref.		
Ph+	28	.7	.4-1.3	.2
Status at HSCT				
CR1	28	Ref.		
CR2/CR3	55	2.02	.9-4.3	.07
Active disease	40	3.1	1.4-6.7	.005
Preparative regimen				
RIC	32	Ref.		
HD	91	1.1	.6-1.8	.8
Allotype				
Matched unrelated	45	Ref.		
Matched related	65	.7	.5-1.2	.2
Cord blood	7	.8	.3-2.2	.6
Mismatched related	6	1.6	.6-4.2	.3
Time to relapse				
>6 mo	42	Ref.		
≤6 mo	81	2.05	1.2-3.4	.007
Site of relapse				
Systemic	99	Ref.		
Isolated EM	24	.8	.4-1.4	.4

RIC indicates reduced-intensity conditioning; HD, high-dose conditioning.
* Palliative group was excluded.
† Palliative group and nonassessable patients excluded.

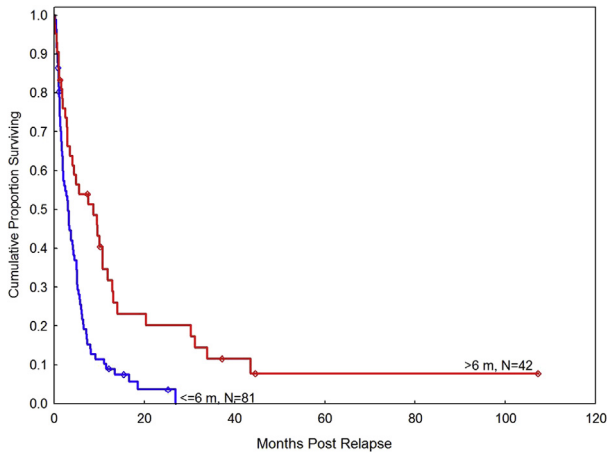

Figure 1. Comparison of OS between patients who relapsed within 6 months of HSCT and those who relapsed after 6 months.

Among 38 patients with any EM relapse, 61% (n = 23) had EM disease before HSCT. The central nervous system (CNS) was the most common site of EM relapse (n = 25), followed by mediastinal masses/lymph node involvement (n = 8) and testicular involvement (n = 2). Five patients had more than 1 site of EM relapse. Among the 25 patients with CNS relapse, 52% (n = 13) had CNS disease before their transplantation. The median time from transplantation to relapse was similar among the patients with isolated relapse (7 months; range, 1 to 28) compared with patients with systemic relapse (4 months; range, 1 to 38), $P = .3$.

Among the 24 patients with isolated EM relapse, 20 received treatment as described: radiation ± intrathecal therapy (n = 6), DLI (n = 1), chemotherapy ± radiotherapy/intrathecal (n = 11), and chemotherapy followed by HSCT (n = 2). CR to salvage therapy was noted in 70% of patients (n = 14), but 50% relapsed again and ultimately died from disease-related complications. Among the 7 patients who achieved a durable CR, only 3 patients with isolated CNS relapse remain alive and disease free, all having received systemic therapy (1 patient after chemotherapy and radiotherapy followed by a second transplantation and 2 patients after chemotherapy and radiotherapy only). Three patients -died of treatment-related complications while in remission, and 1 was lost to follow-up. There was no significant difference in survival among patients with isolated EM relapse compared with those with combined BM/EM relapse or those with isolated BM relapse: 6-month OS, 44% (95% CI, 24 to 63), 29% (95% CI, 9 to 52), and 34% (95% CI, 24 to 44), respectively.

Outcomes Associated with IST Withdrawal

Sixty-six patients had IST withdrawal at the time of relapse. Of these patients, 9 did not receive any further antileukemic therapy, did not show any response to IST withdrawal, and died of disease progression. Fifty-four patients received salvage therapy in addition to IST withdrawal, among which 44% (n = 24) attained a CR with first-line salvage. However, only 2 patients remain alive and disease-free (1 patient after a second transplantation and 1 patient still receiving intensive chemotherapy), whereas 45 died of persistent disease and 7 died from various treatment-related complications. Three patients were lost to follow-up. Twenty-six percent of patients who had IST withdrawal at time of relapse (n = 17) developed GVHD, with 17% (n = 11) occurring within 3 months of stopping IST and 9% (n = 6) developing after subsequent DLI. The incidence of acute GVHD grades II to IV was 23% (n = 15) and grades III to IV was 3% (n = 2). Two patients developed chronic GVHD.

Assessment of the EBMT Scoring System

A recent report from the EBMT analyzing the prognostic factors that affected postrelapse OS indicated that by using a combination of 3 prognostic factors (disease status at the time of transplantation, interval from transplantation to relapse, and number of peripheral blasts at the time of relapse), 3 different prognostic groups for survival could be identified[9]. When this EBMT prognostic score was applied to the patients in our study who underwent tranplantation in remission, we found a similar trend: the median survival rates in patients with 0, 1, 2, and 3 risk factors were 10 months, 6 months, 3 months, and 2 months, respectively.

DISCUSSION

We present data on a large cohort of adult ALL patients who relapsed after HSCT from a single center and were treated over an 18-year period. The relatively large sample size and long follow-up allowed us to investigate key issues in this patient population that has not been well studied. One important observation is the incidence, nature, and prognosis of isolated EM relapses after HSCT. Among the 381 transplantations performed for ALL during this study period, we report an EM relapse rate of 10%, with an isolated EM rate of 6%, which are very similar to that reported in the literature [16-18]. However, unlike other studies in the literature on EM relapse after allogeneic transplantation [17], we found no differences in survival outcomes after isolated EM relapse compared with systemic relapse (Table 3).

Importantly, our study was limited to only ALL. The inclusion of patients with other hematological malignancies, in particular acute myelogenous leukemia (AML), may account for the conflicting results. A recent study by a Minnesota group looking solely at patients with AML and EM relapse after HSCT demonstrated a significantly better probability of 6-month survival in the patients with isolated EM relapse (69%) compared with those with combined BM and EM relapse (8%) or those with BM relapse alone (27%) ($P < .01$) [19]. In contrast, we report survival rates of 44% (95% CI, 24 to 63), 29% (95% CI, 9 to 52), and 34% (95% CI, 24 to 44) in the isolated EM, combined BM/EM, and isolated BM relapse groups, respectively ($P = .8$). The contrast in the findings between the studies suggests that the prognosis of isolated EM relapse after HSCT depends on the disease subtype and may be poorer in patients with ALL compared with AML. Differences in disease biology, including the propensity of ALL to infiltrate immunological sanctuary sites such as the CNS and testis, as well as variation in treatment, including the up front use of CNS prophylaxis in ALL, all likely contribute to the different outcomes for ALL and AML. The treatment options for isolated EM relapse have typically included radiotherapy and/or intrathecal therapy; the role of systemic therapy in this setting remains less clear. In our study, all 3 long-term survivors with isolated EM disease received some form of systemic therapy.

We also attempted to draw some conclusions regarding the optimal management of IST at the time of relapse. Discontinuation of IST with the aim of inducing a graft-versus-leukemia effect has been a common practice in patients who relapse after allogeneic transplantation.

Although a few case reports have suggested the possibility of inducing long-term remission with IST withdrawal alone [20,21], larger studies looking at this have suggested minimal efficacy for this approach, especially in patients with acute leukemia [22]. One limitation of trying to evaluate the impact of IST withdrawal in a retrospective study is the fact that IST withdrawal is often used in combination with antileukemia therapy rather than as a sole modality of treatment. In our study, 11 of 17 patients who developed GVHD after IST withdrawal developed remission to their first-line salvage therapy. The close proximity between the timing of IST withdrawal, the development of GVHD, and the use of antileukemia therapy in these patients, however, makes it difficult to ascertain the specific contribution of each event to graft-versus-leukemia and leukemia response. Nevertheless, in our study, the findings that none of the 9 patients who had IST withdrawal alone attained remission and the fact that only 2 patients achieved long-term remission among the 66 patients with IST withdrawal (both of whom had received other antileukemic therapy) suggest a likely minimal efficacy of such a strategy in this patient population. Furthermore, there is the concern of inducing GVHD after IST withdrawal, particularly in patients who relapse early after HSCT or in patients who receive further chemotherapy that may induce a cytokine-abundant environment. We noted an acute grades II to IV GVHD rate of 17% after IST discontinuation. The subsequent salvage treatment, which commonly includes steroids in ALL, also likely impacts the GVHD rate. Thus, the complexity of the patient at time of transplantation makes it difficult for us to make definitive conclusions. However, given the potential life-threatening toxicities associated with GVHD and the minimal impact of IST withdrawal on disease control, it is reasonable to continue low-dose immune suppression at time of relapse.

The inclusion in our study of patients over an 18-year period provided a reflection of the paradigm shift in treatment strategies over time in this field. This included the increased use of noncytotoxic therapeutic agents, such as monoclonal antibodies and TKI therapies, during the last decade. The retrospective nature of our study, however, precluded the ability to determine the optimal salvage regimen or agents. The best survival was seen in patients who received a second transplantation (Table 2), although these findings are likely biased by the fact that these patients had good response to salvage therapy and needed to have survived long enough to receive their second transplantation. More importantly, although a second transplantation is likely the only curative options for these patients, the generally high treatment-related mortality and poor outcomes of second transplantations for relapsed ALL [15] make it difficult to justify this procedure currently except for possibly a small selected subgroup of patients or in the context of clinical trials with novel therapeutic interventions. Whether the advent of promising novel agents including monoclonal antibody therapies will lead to an improvement in outcomes remains as yet unclear and will depend on the results of prospective studies in this field.

In our study, the median OS after relapse was 4 months and the 2-year OS rate was 10%, which are very similar to the registry data reported by the EBMT group (median OS after relapse of 5.5 months and 2-year OS rate of 16% ± 2%)[9]. In addition, in our univariate analysis for survival, our study findings were consistent with that of EBMT registry data with respect to the prognostic value of relapse-related characteristics, including active disease at the time of first HSCT (hazard ratio = 1.8, $P = .01$) and short duration of relapse (≤6months) from first HSCT (hazard ratio = 2.05, $P = .007$) as well as the lack of prognostic significance for disease-related characteristics, such as immunophenotype and cytogenetic classification at diagnosis (Table 3). Finally, we were able to corroborate the EBMT scoring system to prognosticate outcome after transplantation relapse. We noted a significant difference in median OS for the good-prognosis group (score 0/1) compared with the poor-prognosis group (score 2/3) (median OS of 7 months versus 3 months, $P = .009$). However, given the constraints of a retrospective analysis, we cannot exclude the possibility that patients with shorter time to relapse and more extensive prior therapy to transplantation might have been more likely offered a palliative approach, hence biasing our findings.

In conclusion, survival of patients with ALL who relapse after transplantation is extremely poor, with no difference in outcome between patients with isolated EM versus systemic relapse, suggesting that all relapse should be treated systemically. Furthermore, abrupt discontinuation of immune suppression at time of relapse does not result in clinical benefit and may result in more GVHD; thus, continued low-dose immune suppression may be the optimal approach. Finally, reinduction and second transplantation in a highly selected patient group offers the best chance for prolonged survival. Ultimately, these data emphasize the need for continued research in preventing, rather than treating, relapse. Increased use of minimal residual disease monitoring, preemptive immunotherapeutic interventions, and posttransplantation maintenance strategies should be considered [23].

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