ASBMT
American Society for Blood and Marrow Transplantation

Extramedullary Relapse of Acute Myelogenous Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation: Better Prognosis Than Systemic Relapse

Melhem Solh,[1,2] Todd E. DeFor,[3] Daniel J. Weisdorf,[1,2] Dan S. Kaufman[1,2]

Allogeneic hematopoietic cell transplantation (HSCT) is considered a curative treatment for acute myelogenous leukemia (AML). Extramedullary relapse after HSCT for AML is a rare event and is less well defined than systemic, hematologic relapse. We retrospectively studied all patients with AML (n = 436) who underwent HSCT at the University of Minnesota between 1996 and 2008 who developed either a bone marrow (BM) or extramedullary (EM) relapse, and examined the incidence and risk factors for BM and EM relapse. Of 128 patients who relapsed post-HSCT, 25 had relapse in EM sites, either isolated (n = 13) or with concurrent BM relapse (n = 12). Relapse sites included bone (n = 1), central nervous system (n = 6), gastrointestinal (n = 4), lymphatic (n = 4), skin (n = 5), genitourinary (n = 1), pulmonary (n = 1), and soft tissue (n = 3). The time to relapse was longer in the EM sites (median, 328 days vs 168 days). Patients with EM relapse were more likely to have had preceding acute graft-versus-host disease (GVHD) (77% vs 49%; $P = .03$) or chronic GVHD (46% vs 15%; $P = .02$) compared with those with BM relapse. The 6-month survival postrelapse was significantly better in patients with isolated EM relapse (69%) compared with those with combined EM and BM relapse (8%) or those with BM relapse alone (27%) ($P < .01$). Compared with local therapy alone, systemic therapy yielded better 6-month survival in patients with EM relapse. This study suggests differing pathogenesis of BM relapse versus EM relapse of AML after allogeneic HSCT. GVHD and its accompanying graft-versus-leukemia effect may better protect BM sites, but patients with EM relapse have better responses to combined therapy and improved survival compared with those with BM relapse.

Biol Blood Marrow Transplant 18: 106-112 (2012) *© 2012 American Society for Blood and Marrow Transplantation*

KEY WORDS: Extramedullary, Relapse, Leukemia, Transplantation

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is considered a standard treatment and potentially curative for a significant subset of patients with acute myelogenous leukemia (AML) [1]. However, disease relapse remains the most common cause of treatment failure post-HSCT [2]. Although the incidence of leukemia relapse in intermediate and high-risk patients with AML is reduced after allogeneic HSCT compared with conventional consolidation chemotherapy [3-5], a significant number of extramedullary (EM) relapses have been reported [6-8]. EM relapse has been reported in diverse sites, including the brain [9], breast [10], head and neck [11], gastrointestinal (GI) tract [12], liver [13], urogenital tract [12], spinal canal [11], bone [10,12], skin [14], chest [13], and peritoneum [15]. The median time from HSCT to EM relapse is longer than that from HSCT to bone marrow (BM)-only relapse; Lee et al. [6] reported a median time of 13.5 months post-HSCT in patients with EM relapse, compared with 6.1 months in those with BM-only relapse. Although EM relapse remains a rare and devastating event, little is known about its incidence, biology (eg, sanctuary sites, uneven graft-vs-leukemia [GVL] effect) [16,17], risk factors (differing cytogenetic or morphologic French-American-British [FAB] category), treatment, and outcomes. Other reported

From the [1]Blood and Marrow Transplant Program; [2]Divsion of Hematology, Oncology and Transplantation; and [3]Biostatistics and Bioinformatics Core, Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota.

This study was presented at American Society of Bone Marrow Transplantation Tandem Meeting, Honolulu, Hawaii February, 17, 2011.

Financial disclosure: See Acknowledgments on page 111.

Correspondence and reprint requests: Melhem Solh, MD, Division of Hematology, Oncology and Transplantation, University of Minnesota, Mayo Mail Code 480, 420 Delaware Street SE, Minneapolis, MN 55455 (e-mail: solhx001@umn.edu).

Received April 12, 2011; accepted May 31, 2011

© 2012 American Society for Blood and Marrow Transplantation

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.05.023

factors associated with increased risk of EM relapse include disease status at HSCT and T cell depletion of the hematopoietic cell graft [6].

We investigated the incidence of medullary and EM relapse among 436 consecutive adult and pediatric patients with AML who underwent allogeneic HSCT between 1996 and 2008 at the University of Minnesota to identify any differences between relapse in the BM and EM sites in terms of risk factors, response to therapy, and overall outcome.

PATIENTS AND METHODS

Study Design and Patient Selection

For this single-institution retrospective cohort study, we reviewed the University of Minnesota's Blood and Marrow Transplant Database to identify patients with AML who experienced relapse after undergoing allogeneic HSCT between January 1996 and December 2008. The relapsed patients were divided into 3 subgroups: isolated BM-only relapse (n = 103), EM relapse without concurrent BM relapse (n = 13), and EM relapse with concurrent BM relapse (n = 12). All patients who experienced EM relapse underwent a BM biopsy and aspiration for evaluation of the diagnosis of EM relapse. EM relapse was confirmed by a needle or excisional biopsy in all cases and a thorough workup, including detailed physical examination, testicular examination, and total body imaging (ie, computed tomography or positron emission tomography scan) to investigate for other sites of EM leukemia. Patients' records were also reviewed for the presence of EM leukemia before HSCT.

Patients undergoing HSCT while in first complete remission (CR1) were classified as standard risk; all other patients were considered high risk. Cytogenetic risk grouping of the EM relapse patients was assigned according to Southwest Oncology Group criteria. AML subtype was assigned according to the FAB classification system. Systematic and prospectively collected information from the Bone Marrow Transplant Program Database was supplemented by a review of medical records. This study was approved by the University of Minnesota's Institutional Review Board.

Treatment Characteristics

Patients reviewed for this analysis received either full myeloablative conditioning or reduced-intensity conditioning (RIC) before undergoing allogeneic HSCT. Eligibility criteria for RIC included age ≥55 years for a matched related donor (MRD) transplant or ≥45 years for an umbilical cord blood (UCB) transplant, presence of significant comorbidity, and history of previous HSCT or extensive previous therapy. Most of the patients who relapsed received a total body irradiation (TBI)-based conditioning regimen, with low-dose TBI (200 cGy) for RIC and high-dose TBI (1320 cGy) for full myeloablative conditioning. RIC regimens included busulfan (Bu) 2 mg/kg orally every 12 hours for 4 doses on days −8 and −7, fludarabine (Flu) 40 mg/m^2 i.v. daily from days −6 to −2, and TBI 200 cGy on day −1 (Bu/Flu/TBI) and cyclophosphamide (Cy) 50 mg/kg on day −6 with Flu and TBI as above, with or without antithymocyte globulin (ATG) (Cy/Flu/TBI ± ATG). Full-intensity myeloablative regimens included Cy 60 mg/kg i.v. on days −6 to −5 and TBI 1320 cGy over 8 fractions on days −4 to −1 (Cy/TBI), Bu 16 mg/kg over 16 doses on days −9 to −6, Cy 50 mg/kg/day on days −5 to −2 (Bu/Cy), and Flu 25 mg/m^2 on days −8 to −6 plus Cy/TBI as above (Flu/Cy/TBI). All patients received granulocyte-colony stimulating factor 5 μg/kg/day i.v. starting day on 0 and continuing until the absolute neutrophil count was ≥2500/μL for 2 days.

All patients received graft-versus-host disease (GVHD) prophylaxis in accordance with University of Minnesota protocols during the transplantation period. Institutional GVHD prophylaxis usually includes methotrexate plus cyclosporine for full-intensity transplantation and cyclosporine plus mycophenolate for RIC and UCB transplantation.

Donor Chimerism

Donor chimerism was determined serially on marrow and/or blood samples obtained after HSCT. Chimerism analysis was performed using quantitative polymerase chain reaction of informative polymorphic variable-number tandem repeat or short tandem repeat regions in recipient and donor, as described previously [18].

Study Definitions and Statistical Analysis

The time to AML relapse was defined as the interval between day 0 of HSCT and the relapse of leukemia. Statistical comparisons of baseline factors across types of relapse were done using the chi-square or Fisher exact test for categorical variables and the general Wilcoxon test for continuous factors. The cumulative incidence estimates for leukemia relapse were determined by treating death as a competing risk [19] and were compared using the log-rank test. Survival through 6 months postrelapse was estimated using the Kaplan-Meier method. Cox regression models were used to investigate the difference in survival by medullary and EM relapse controlling for confounding factors. Factors that were included in the regression models were donor type (MRD vs mismatched related donor; unrelated donor vs UCB), previous GVHD (both acute and chronic), time from HSCT to relapse, cytomegalovirus (CMV) serostatus (negative vs positive), disease status at HSCT (CR1

vs CR2 vs CR3+/relapse), conditioning (myeloablative vs nonmyeloablative), and age. All factors were tested for the proportional hazards assumption. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

CR was defined as the absence of disease on clinical, radiologic, and pathological evaluation. Partial remission (PR) was defined as a ≥50% reduction in sites of known disease. Failure to achieve PR was defined as persistent disease (PD). Local therapy was defined as surgical resection and/or local radiation to the involved area. Patients who received intrathecal chemotherapy for central nervous system (CNS) leukemia without other systemic therapy were considered to have received local therapy. Systemic therapy included donor lymphocyte infusion (DLI), chemotherapy, and second HSCT. Combined therapy was defined as administration of both local and systemic therapy. Patients were considered to have undergone surgery as a therapeutic modality only if surgical excision was done for treatment intention (ie, removal of a mass) or if an excisional biopsy was obtained in which the whole lesion was excised, with no positive margins on pathology.

RESULTS

Patient Characteristics

Between 1996 and 2008, 436 adult and pediatric patients with AML underwent allogeneic HSCT. Of these 436 patients, 128 experienced relapse; the cumulative incidence of relapse at 5 years was 35% (95% confidence interval [CI], 30%-40%). Of these, 103 had BM-only relapse, 13 had EM relapse with concurrent BM relapse, and 12 had EM relapse without concurrent BM relapse. The median age of the patients who relapsed was 43 years (range, 1-70 years). The 3 relapse groups did not differ in terms of CMV donor–recipient serostatus, hematopoietic cell source (BM, peripheral blood, or UCB), donor source (related or unrelated), conditioning intensity, and GVHD prophylaxis. A significantly higher proportion of the patients in the isolated EM relapse group had previous grade II-IV acute GVHD (77%), compared with 49% in BM relapse–only group and 25% in the EM plus concurrent BM relapse group ($P = .03$). Of the 25 patients with EM relapse, 5 had normal cytogenetics, 3 had favorable cytogenetics, 14 had unfavorable cytogenetics, and 3 had undetermined prognostic cytogenetics. Patient, disease, and transplant characteristics are summarized in Table 1.

Patients with EM Relapse

Table 2 summarizes the site distribution, treatment, and outcomes for patients with EM relapse with or without marrow relapse. The CNS, GI tract, skin, and soft tissue were the most common sites of EM relapse. Only 5 of the 25 patients with EM relapse had EM leukemia before undergoing HSCT, with 1 case each involving the skin, CNS, lymph nodes, soft tissue, and mediastinum. All of these patients relapsed in the same site as the previous leukemia, whereas the patient with leukemia cutis before HSCT had an additional relapse in the CNS post-HSCT. Among the 6 patients with CNS involvement, 2 had a brain mass, 2 had a spinal mass, and 2 had only cerebrospinal fluid involvement. In the 4 patients with GI involvement, sites included the pharynx, parotid gland, jejunum, and duodenum. Involved soft tissue sites included breast and labia (n = 1), paraspinal tissue (n = 1), and thigh, pelvis, and popliteal fossa (n = 1).

Eight patients received local therapy only, including local radiation (n = 5), surgical resection (n = 2), and intrathecal chemotherapy (n = 1). Six patients received DLI, 3 patients had chemotherapy followed by a second HSCT, 2 patients received no therapy, 1 patient had withdrawal of immunosuppression, and the rest received chemotherapy using varying agents (eg, gemtuzumab ozagamycin, cytarabine, fludarabine, hydroxyurea). Eight patients experienced a second relapse after achieving a CR after treatment of the first relapse. Two patients with concurrent EM and medullary relapse experienced their second relapse in the BM only. In the 6 patients with isolated EM relapse who achieved a CR and later relapsed again, the involved sites were pleura (previous relapse site, small bowel), humerus, and soft tissue (previous relapse site, parotid gland), CNS (previous relapse site, CNS), BM (previous relapse site, CNS), and 2 soft tissue (previous relapse sites, soft tissue in various locations). Among the 8 patients who experienced a second relapse, 5 patients received chemotherapy plus DLI as previous therapy.

Survival Postrelapse

The 6-month overall survival (OS) postrelapse was 30% for all 128 patients who relapsed (Table 3). As shown in Figure 1, patients with isolated EM relapse had a better 6-month OS (69%; 95% CI, 37%-87%) compared with patients with BM-only relapse (27%; 95% CI, 19%-36%) and those with EM plus concurrent medullary relapse (8%; 95% CI, 1%-31%) ($P < .01$). Patients with chronic GVHD before relapse had improved OS after relapse, perhaps due to a persistent (although incomplete) GVL effect. Early onset of relapse (<6 months post-HSCT) was associated with poor outcome.

The Cox regression analysis of factors associated with improved survival for AML relapse post-HSCT identified the following favorable factors: isolated

Table 1. Demographic Data for Patients with Relapsed AML Post-HSCT (n = 128)

Factor	Marrow Relapse	EM without Concurrent BM Relapse (n = 13)	EM with Concurrent BM Relapse (n = 12)	Patients with Post-HSCT Relapse (n = 128)	*P* Value
Age, years, median (range)	44 (1-70)	27 (1-57)	35 (1-56)	43 (1-70)	.20
Time to relapse, days, median (range)	168 (21-2273)	328 (30-2329)	146 (21-813)	168 (21-2329)	.42
Male sex	56 (54)	7 (54)	8 (67)	71	.71
AML, n (%)	103	13	12	128	.93
FAB0	5 (5)	1 (8)	1 (8)	7	
FAB1	13 (13)	0	1 (8)	14	
FAB2	24 (23)	3 (23)	3 (25)	30	
FAB3	3 (3)	0	1 (8)	4	
FAB4	9 (9)	2 (15)	1 (8)	12	
FAB5	9 (9)	4 (31)	2 (17)	15	
FAB6	4 (4)	0	1 (8)	5	
FAB7	3 (3)	0	0	3	
AML not otherwise specified	33 (32)	3 (23)	2 (17)	38	
Disease status at HSCT					.87
CR1	44 (43)	6 (46)	5 (42)	55	
CR2	33 (32)	3 (23)	5 (42)	41	
CR3+	7 (7)	2 (15)	1 (8)	10	
Relapse	19 (18)	2 (15)	1 (8)	22	
Conditioning intensity					.61
Myeloablative	55 (53)	8 (62)	8 (67)	71	
RIC	48 (47)	5 (38)	4 (33)	57	
Non-TBI	7 (7)	3 (23)	1 (8)	11	.25
Bu/Flu/TBI	7 (7)	1 (8)	0	8	
Cy/Flu/TBI ± ATG	45 (44)	4 (31)	6 (50)	55	
Cy/TBI	44 (43)	5 (38)	5 (42)	54	
Grade II-IV acute GVHD before relapse	50 (49)	10 (77)	3 (25)	63	.03
Chronic GVHD before relapse	15 (15)	6 (46)	2 (17)	23	.02

EM relapse, MRD, presence of grade II-IV acute GVHD before relapse, and relapse beyond 6 months post-HSCT. CMV serostatus, disease status at time of transplantation (CR1, CR2, or CR3+/relapse), age, conditioning regimen, and regimen intensity were not associated with a change in OS postrelapse.

Table 2. Data for Patients with EM Relapse (n = 25)

Factors	EM without Concurrent BM, n (%) (n = 13)	EM with Concurrent BM, n (%) (n = 12)	Total (n = 25)	*P* Value
Relapse site				.27
Bone	0	1 (8)	1	
CNS	3 (23)	3 (25)	6	
GI	3 (23)	1 (8)	4	
Genitourinary	0	1 (8)	1	
Lymphatic	3 (23)	1 (8)	4	
Pulmonary	0	1 (8)	1	
Skin	1 (8)	4 (33)	5	
Soft tissue	3 (23)	0	3	
EM leukemia before HSCT	5 (38)	3 (25)	8	.47
Type of therapy				.94
Combined	3 (23)	2 (17)	5	
Local	5 (38)	3 (25)	9	
Systemic	4 (31)	6 (50)	9	
None	1 (8)	1 (8)	2	
Surgical resection	5 (38)	2 (17)	7	.23
Response to treatment				.05
CR	10 (77)	3 (25)	13	
PD	2 (15)	7 (58)	9	
PR	1 (8)	2 (17)	3	
Second relapse*	6 (46)	2 (17)	8	.11

*Patients who experienced a second relapse after treatment.

Survival of Patients with EM Relapse

Table 4 summarizes the survival outcomes of patients with EM relapse. In univariate analysis, patients with EM relapse with concurrent BM relapse had significantly lower 6-month OS compared with patients with isolated EM relapse. Patients who received systemic or combined modality therapy for the EM relapse had a better OS compared with those treated with local therapy only.

DISCUSSION

Relapse remains the most common cause of treatment failure in patients with AML undergoing allogeneic HSCT. The incidence of relapse ranges from 20% to 50% depending on disease characteristics [20], donor source [21], and conditioning regimen [22]. The reported incidence of EM relapse after allogeneic HSCT varies widely. Previous retrospective registry data reported 20 of 3071 patients with AML with EM relapse, for an incidence of 0.7% [11]. More recent series based mostly on single institutional reports have reported higher occurrences of EM relapse, ranging from 5% to 12% [6,14,23-26]. In our series of 436 patients with AML, the overall relapse rate was 35%, and the EM relapse rate was 5.7%. EM relapse with or without BM involvement accounted for 20% of the overall initial relapses.

Some previous investigators have attributed the discrepancies in the reported rates of EM relapse

Table 3. OS Postrelapse in Patients with Relapse

Factors	Number of Patients	Number of Deaths	6-Month Survival (95% CI), %	*P* Value
Total	128	90	30 (22-38)	
Type of relapse				<.01
BM only	103	75	27 (19-36)	
EM without concurrent BM	13	4	69 (37-87)	
EM with concurrent BM	12	11	8 (1-31)	
Type of relapse				.32
BM	103	75	27 (19-36)	
EM	25	15	40 (21-58)	
Disease status at HSCT				.18
CR1	55	37	33 (21-45)	
CR2	41	27	34 (20-49)	
CR3+	10	6	40 (12-67)	
Relapse	22	20	9 (2-25)	
Donor type				.04
MRD	45	30	33 (20-47)	
MMRD or URD	13	12	8 (0-29)	
UCB	70	48	31 (21-42)	
Age, years				.77
<40	59	40	32 (21-44)	
≥40	69	50	28 (18-38)	
Acute GVHD before relapse				.07
No	65	42	35 (24-47)	
Yes	63	48	24 (14-35)	
Chronic GVHD before relapse				.04
No	105	78	26 (18-34)	
Yes	23	12	48 (27-66)	
Time to relapse, months				
<6	73	58	21 (12-30)	<.01
≥6	55	32	42 (29-54)	

MMRD indicates mismatched related donor; URD, unrelated donor.

between registry and single-institution reports to underreporting in registry data, as well as longer follow-up in recent series, attributed to longer survival and generally improved outcomes of HSCT [6]. We believe that EM may still be underreported, because asymptomatic EM sites might not be routinely studied clinically and the full extent can only be known at autopsy, which is performed only rarely. It is likely that occult foci of leukemia exist and are resistant to the

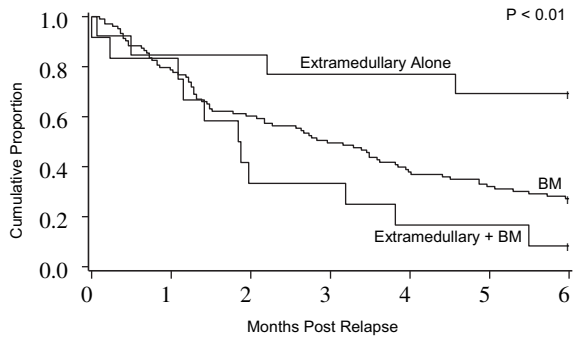

Figure 1. OS of patients with relapsed AML post-HSCT by type of relapse. *P* values are for comparison for any difference between the 3 survival curves. Looking at the 3 pairwise comparisons, the only 2 that are significant at the $P = .05$ level are EM versus BM alone and EM versus BM plus EM.

Table 4. OS after HSCT in Patients with EM Relapse

Factors	Number of Patients	Number of Deaths	6-Month Survival (95% CI), %	*P* Value
Total	25	15	40 (21-58)	
Type of relapse				<.01
EM without concurrent BM	13	4	69 (37-87)	
EM with concurrent BM	12	11	8 (1-31)	
Relapse site				.62
CNS	5	4	20 (1-58)	
EM	19	10	47 (24-67)	
Testis	1	1		
EM leukemia before HSCT				.26
No	17	9	47 (23-68)	
Yes	8	6	25 (4-56)	
Therapy				<.01
Combined	5	3	40 (5-75)	
Local	9	6	33 (8-62)	
Systemic	9	4	56 (20-80)	
None	2	2		
Response to therapy				<.01
CR	13	3	77 (44-92)	
PD	9	9	0	
PR	3	3		

GVL effect. Such foci are identified clinically either incidentally or when symptoms arise, but the exact frequency of this after HSCT is not known.

Various factors have been suggested to contribute to the risk of EM relapse of AML after allogeneic HSCT. Simpson et al. [23] reported a higher incidence of EM relapse after busulfan-containing conditioning compared with total body irradiation (TBI)-based conditioning, but another study could not confirm this finding [27]. We observed a similar incidence of EM relapse after TBI-based conditioning and non–TBI-based conditioning, even after RIC. Other factors previously suggested to predict EM relapse include AML subtype (FAB M4 and M5), abnormal karyotype, and disease status at the time of HSCT [6,7]. However, most of these reported predictors of EM relapse are from small retrospective series, and the reproducibility of these findings is questionable. Our data show a higher incidence of acute and chronic GVHD in patients with EM relapse compared with patients with BM relapse, a finding confirmed in other reports [28]. This suggests that the pathogenesis of EM relapse might differ from that of the more common BM relapse, and suggests that immune surveillance through the GVL effect may be less effective in EM sites.

The timing from HSCT to EM relapse has been consistently reported to be longer than the time from HSCT to BM relapse. We and others have reported a median time to EM relapse of 11-13 months, compared with 3-6 months for BM relapse [6,16,25,27,28]. Importantly, censoring of surveillance may accompany a BM relapse that might subsequently overlook or preemptively treat an unrecognized EM

relapse. In addition, differing expression of adhesion molecules (e.g. $CD56^+$ cells) on surviving leukemic cells might facilitate adherence to dermal fibroblasts and thus to sites of isolated EM relapse [29,30]. In addition, EM sites might serve as sanctuary havens for the dormant leukemic clone after HSCT. These sanctuary sites, protected from chemotherapy or immune responses, might give the leukemic cells an opportunity for progressive overgrowth [16,31]. Cytotoxic $CD8^+$ T cells are the main mediators of the GVL effect and are highly more concentrated in the BM compared with the peripheral tissues [32]. Homing of T cells is regulated by a host of cell surface molecules (eg, selectins) that direct T cells to specific sites. Thus, relapse in EM sites may occur in part because such sites are not well protected by the T cells [33].

The treatment of EM relapse remains a challenge, given the lack of standardized strategies for management. Historically, treatment has consisted of local therapy, such as surgical excision and/or radiation, and systemic therapy including DLI, second HSCT, and/or chemotherapy. These modalities can be used individually or in combination. Most patients with EM relapse develop BM disease without systemic treatment. This argues for providing systemic therapy for all such patients [7,11,34], a longstanding principle of management in intensification strategies for acute lymphoblastic leukemia. Isolated EM relapse is associated with better survival than BM relapse when aggressive treatment is provided [28].

In conclusion, our study demonstrates that isolated EM relapse of AML after allogeneic HSCT is relatively common. EM relapse occurs later than systemic relapse, and EM relapse without concurrent BM involvement is associated with better prognosis. EM relapse is more common in patients with GVHD, suggesting that the GVL effect might be less protective in these EM sites. Additional larger studies are needed to define risk factors and prognostic indicators and to establish treatment guidelines.

ACKNOWLEDGMENTS

Financial disclosure: The authors have no conflicts of interest to disclose.

REFERENCES

1. Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol*. 2011;29:487-494.
2. Schlenk RF, Dohner K, Mack S, et al. Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian trial AMLHD98A. *J Clin Oncol*. 2010;28:4642-4648.
3. Giralt SA, Champlin RE. Leukemia relapse after allogeneic bone marrow transplantation: a review. *Blood*. 1994;84:3603-3612.
4. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *N Engl J Med*. 1995;332:217-223.
5. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358:1909-1918.
6. Lee KH, Lee JH, Choi SJ, et al. Bone marrow vs extramedullary relapse of acute leukemia after allogeneic hematopoietic cell transplantation: risk factors and clinical course. *Bone Marrow Transplant*. 2003;32:835-842.
7. Cunningham I. Extramedullary sites of leukemia relapse after transplant. *Leuk Lymphoma*. 2006;47:1754-1767.
8. Kikushige YK, Takase K, Sata K, et al. Repeated relapses of acute myelogenous leukemia in the isolated extramedullary sites following allogeneic bone marrow transplantations. *Intern Med*. 2007;46:1011-1014.
9. Oshima K, Kanda Y, Yamashita T, et al. Central nervous system relapse of leukemia after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2008;14:1100-1107.
10. Schafer H, Bader P, Kaiserling E, et al. Extramedullary relapses at uncommon sites after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2000;26:1133-1135.
11. Bekassy AN, Hermans J, Gorin NC, et al. Acute and Chronic Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. Granulocytic sarcoma after allogeneic bone marrow transplantation: a retrospective European multicenter survey. *Bone Marrow Transplant*. 1996;17:801-808.
12. Fleming DR, Greenwood ME, Garrison J, et al. Lymphocyte infusion for delayed extramedullary relapse of acute leukemia following bone marrow transplantation. *Leuk Lymphoma*. 1996;21:525-528.
13. De la Camara R, Figuera A, Steegmann JL, et al. Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia. Results from a single institution. *Bone Marrow Transplant*. 1992;9:433-438.
14. Michel G, Boulad F, Small TN, et al. Risk of extramedullary relapse following allogeneic bone marrow transplantation for acute myelogenous leukemia with leukemia cutis. *Bone Marrow Transplant*. 1997;20:107-112.
15. Riseberg DA, Mulvey KP, Dahut WL, et al. Late extramedullary relapse following bone marrow transplant for AML presenting as acute renal failure and leukemic ascites. *Bone Marrow Transplant*. 1994;14:1009-1010.
16. Au WY, Kwong YL, Lie AK, et al. Extra-medullary relapse of leukemia following allogeneic bone marrow transplantation. *Hematol Oncol*. 1999;17:45-52.
17. Lee KH, Lee JH, Kim S, et al. High frequency of extramedullary relapse of acute leukemia after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2000;26:147-152.
18. Barker JN, Weisdorf DJ, DeFor TE, et al. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood*. 2003;102:1915-1959.
19. Lin DY. Non-parametric inference for cumulative incidence functions in competing risks studies. *Stat Med*. 1997;16:901-910.
20. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA*. 2009;301:2349-2361.
21. Sierra J, Storer B, Hansen LA, et al. Unrelated donor marrow transplantation for acute myeloid leukemia: an update of the Seattle experience. *Bone Marrow Transplant*. 2000;26:397-404.
22. Aoudjhane M, Labopin M, Gorin NC, et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA-identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with

acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). *Leukemia*. 2005;19:2304-2312.
23. Simpson DR, Nevill TJ, Shepherd JD, et al. High incidence of extramedullary relapse of AML after busulfan/cyclophosphamide conditioning and allogeneic stem cell transplantation. *Bone Marrow Transplant*. 1998;22:259-264.
24. Stadler M, Dierich H, Damman E, et al. Extramedullary acute leukemias prior to and after allogeneic hematopoeitic stem cell transplantation: a single-center study. ASH Annual Meeting Abstracts. *Blood*. 2008;112:3262.
25. Kata D, Kyrez-Krzemien S, Czerw T, et al. Incidence, treatment and outcome of isolated extramedullary relapse after allogeneic hematopoietic stem cell transplantation for acute lymphoblastic and myeloid leukemias: single center experience with 324 patients. ASH Annual Meeting Abstracts. *Blood*. 2008;112:4302.
26. Porter DL, Alyea EP, Antin JH, et al. NCI First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: Report from the Committee on Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2011;16:1467-1503.
27. Blum W, Penza S, Farag S, et al. Incidence of extramedullary relapse of acute myeloid leukemia following transplantation with busulfan-based conditioning regimens. ASH Annual Meeting Abstracts. *Blood*. 2004;104:5123.
28. Shimoni A, Rand A, Hardan I, et al. Isolated extramedullary relapse of acute leukemia after allogeneic stem cell transplantation: different kinetics and better prognosis than systemic relapse. ASH Annual Meeting Abstracts. *Blood*. 2008;112:2148.
29. Kobayashi M, Imamura M, Soga R, et al. Establishment of a novel granulocytic sarcoma cell line which can adhere to dermal fibroblasts from a patient with granulocytic sarcoma in dermal tissues and myelofibrosis. *Br J Haematol*. 1992;82:26-31.
30. Kuwabara H, Nagai M, Yamaoka G, et al. Specific skin manifestations in CD56-positive acute myeloid leukemia. *J Cutan Pathol*. 1999;26:1-5.
31. Ruiz-Arguelles GJ, Gomez-Almaguer D, Vela-Ojeda J, et al. Extramedullary leukemic relapses following hematopoietic stem cell transplantation with nonmyeloablative conditioning. *Int J Hematol*. 2005;82:262-265.
32. Chong G, Byrnes G, Szer J, et al. Extramedullary relapse after allogeneic bone marrow transplantation for haematological malignancy. *Bone Marrow Transplant*. 2000;26:1011-1015.
33. Sackstein R. A revision of Billingham's tenets: the central role of lymphocyte migration in acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2006;12(Suppl 1):2-8.
34. Byrd JC, Edenfield WJ, Shields DJ, et al. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. *J Clin Oncol*. 1995;13:1800-1816.