Extramedullary relapse of acute myeloid leukemia following allogeneic hematopoietic stem cell transplantation: incidence, risk factors and outcomes

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ABSTRACT

Extramedullary relapse after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia is a contributor to post-transplant mortality but risk factors for, and outcomes of, this condition are not well characterized. We analyzed 257 consecutive patients undergoing allogeneic stem cell transplantation for acute myeloid leukemia at our institution to characterize extramedullary relapse, identify predictive variables and assess outcomes. The 5-year cumulative incidence of isolated extramedullary or bone marrow relapse was 9% and 29%, respectively. Extramedullary relapse occurred later than marrow relapse and most frequently involved skin and soft tissue. Factors predictive of extramedullary relapse after transplantation included previous extramedullary disease, French-American-British classification M4/M5 leukemia, high risk cytogenetics, and advanced disease status at the time of transplantation. Children were more likely than adults to develop extramedullary relapse, a finding probably explained by an overrepresentation of extramedullary disease prior to transplantation and M4/M5 leukemia in children. Acute graft-*versus*-host disease was not protective against relapse. Unlike medullary relapse, chronic graft-*versus*-host disease was not protective against extramedullary relapse. The survival rate after extramedullary relapse was 30% at 1 year and 12% at 2 years. Extramedullary relapse is a significant contributor to mortality after allogeneic transplantation for acute myeloid leukemia and appears to be resistant to the immunotherapeutic effect of allogeneic grafting. Effective strategies for patients with extramedullary relapse are needed to improve outcomes after transplantation.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a potentially curative treatment for acute myeloid leukemia (AML).[1] However post-HSCT relapse remains an important cause of treatment failure with relapse rates ranging from 30% to 70%,[2-5] depending on a number of factors such as disease status at the time of transplantation, donor source, conditioning regimen, and T-cell content of the graft.[4,6] Extramedullary relapses are known to occur post-HSCT, either as isolated sites of relapse or in combination with marrow relapse,[7-9] and usually result in death.[10,11] Although risk factors for extramedullary disease/relapse have been described in newly diagnosed leukemia patients,[12] there have been few studies supporting the extrapolation of these factors to the post-HSCT setting. Despite the potential importance of post-HSCT extramedullary relapse as a determinant of outcomes, the incidence, risk factors, and treatment of this condition are not well understood, especially in light of the many changes in HSCT strategies over the past 20 years.

Given the need for a better understanding of post-HSCT extramedullary relapse, we performed a retrospective analysis of patients who underwent HSCT for AML at the University of Michigan from January 2001 through May 2008 to identify factors predisposing patients to extramedullary relapse and analyze their post-relapse outcomes.

Design and Methods

Disease-, transplant- and outcome-related data were collected using protocols approved by the Institutional Review Board. Patients were treated according to clinical protocols approved by our Institutional Review Board and/or institutional care practice guidelines.

Information on the patients and their transplants are shown in Table 1. Patients were classified as having high risk cytogenetics if they had any of the following: 5q-, monosomy 7/7q-, complex cytogenetics or FLT-3 positivity. Myeloablative conditioning regimens included busulfan (12.8 mg/kg IV or oral equivalent) combined with cyclophosphamide (120-200 mg/kg) ± cytarabine (6 g/m^2), fludarabine (140 mg/m^2), or clofarabine (150 mg/m^2), or total body irradiation (1200 cGy) combined with cyclophosphamide (120 mg/kg). Reduced intensity regimens included fludarabine (140 mg/m^2) and either busulfan (6.4 mg/kg IV or oral equivalent) or melphalan (140 mg/m^2). Immunosuppression primarily consisted of a calcineurin inhibitor (tacrolimus or cyclosporine) with methotrexate (5 mg/m^2 on days 1, 3, 6, and 11; n=211) or mycophenolate (20-30 mg/kg/day, maximum 3000 mg/day on days 0-28; n=46). Patients enrolled in graft-*versus*-host (GVHD) prevention clinical trials (n=29) received sirolimus in lieu of methotrexate, or etanercept as additional pro-

 doi:10.3324/haematol.2012.073189
Manuscript received on June 29, 2012.Manuscript accepted on September 12, 2012.
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phylaxis. Extramedullary relapse was biopsy-confirmed in all but one patient, who had obvious progression of proven chloromas that were still present at the time of HSCT. Twenty-four of 26 patients (92%) who had extramedullary disease noted at the time of post-HSCT relapse had bone marrow biopsies confirming the presence (n=2) or absence (n=22) of bone marrow recurrence; the remaining two patients deferred bone marrow evaluation and pursued non-curative supportive care.

Statistical analysis

Overall rates of relapse, as well as rates of isolated bone marrow and extramedullary relapse, were estimated using the cumulative incidence methods of Gray,[13] treating death as a competing risk, and the association of patients' characteristics (except for acute and chronic GVHD) with overall and extramedullary relapse was assessed with the competing risk regression methods of Fine and Gray.[14] The association of acute and chronic GVHD, both of which are time-varying covariates, with both types of relapse was assessed using Cox regression methods. A comprehensive multivariate analysis of risk factors for relapse was not possible due to the number of patients available, thus hazard ratios for relapse are those for univariate analyses.

Results

Patients

We retrospectively analyzed a consecutively treated series of 257 patients who underwent allogeneic HSCT at the University of Michigan between January 1, 2001, and May 31, 2008 (Table 1). All but two of the 31 patients with a history of extramedullary disease prior to HSCT cleared their extramedullary disease prior to allogeneic HSCT as determined by radiographic imaging, spinal fluid analysis,

Table 1. Characteristics of patients with AML stratified by relapse and relapse location.

	All patients	Non-relapse	Any relapse	Bone marrow relapse[b]	Extramedullary relapse[c]
Patients, n.	257	158	99	73	26
Age at diagnosis (years), median (range)	48.1 (0.4-69)	48.6 (0.4-67.9)	47.7 (0.6-69)	48.4 (0.8-69)	34.9 (0.6-65.5)
Male, n. (%)	133 (52%)	84 (53%)	49 (49%)	34 (47%)	15 (58%)
Time from diagnosis to transplant (days), median (range)	184 (15-4042)	192 (15-4042)	179 (18-2662)	179 (18-1762)	174 (30-2662)
Pre-transplant risk factors					
Age ≤18 at diagnosis, n. (%)	40 (16%)	19 (12%)	21 (21%)	12 (16%)	9 (35%)
Extramedullary disease prior to transplant, n. (%)	31 (12%)	18 (11%)	13 (13%)	4 (5%)	9 (35%)
High risk cytogenetics[d], n. (%)	76 (30%)	39 (25%)	37 (37%)	23 (32%)	14 (54%)
FAB M4/M5, n. (%)	83 (32%)	45 (28%)	38 (38%)	25 (34%)	13 (50%)
T-cell markers, n. (%)	87 (34%)	53 (34%)	34 (34%)	22 (30%)	12 (46%)
CD56 expression, n. (%)	37 (14%)	20 (13%)	17 (17%)	10 (14%)	7(27%)
Related donor, n. (%)	127 (49%)	75 (47%)	52 (53%)	40 (55%)	12 (46%)
HLA-matched donore, n. (%)	207 (81%)	118 (75%)	89 (90%)	64 (88%)	25 (96%)
Gender mismatch, n. (%)	115 (45%)	72 (46%)	43 (43%)	31 (42%)	12 (46%)
Stem cell source, n. (%)					
Peripheral blood	208 (81%)	130 (82%)	78 (79%)	57 (78%)	21 (81%)
Bone marrow/umbilical cord blood	49 (19%)	28 (18%)	21 (21%)	16 (22%)	5 (19%)
Disease status at time of transplant, n. (%)					
First and second complete remission	162 (63%)	112 (71%)	50 (51%)	39 (53%)	11 (42%)
Third or beyond complete remission/refractory	95 (37%)	46 (29%)	49 (49%)	34 (47%)	15 (58%)
Transplant risk factors					
Total body irradiation in conditioning, n. (%)	26 (10%)	19 (12%)	7 (7%)	4 (5%)	3 (12%)
Busulfan in conditioning, n. (%)	235 (91%)	142 (90%)	93 (94%)	70 (96%)	23 (88%)
Full intensity conditioning, n. (%)	209 (81%)	129 (82%)	80 (81%)	55 (75%)	25 (96%)
Tacrolimus/methotrexate in GVHD prophylaxis[f]	201 (78%)	119 (75%)	82 (83%)	61(84%)	21 (81%)
Any acute GVHD, n. (%)	147 (57%)	93 (59%)	54 (55%)	39 (53%)	15 (58%)
Skin only	72 (28%)	45 (28%)	27 (27%)	19 (27%)	8 (31%)
Visceral ± skin	75 (29%)	48 (30%)	27 (27%)	20 (27%)	7 (27%)
Time to acute GVHD onset (days), median (range)	35 (7-162)	35 (7-162)	34 (10-118)	35 (10-118)	28 (13-99)
Chronic GVHD, n (%)	122 47%)	90 (57%)	32 (32%)	15 (21%)	17 (65%)
Post-transplant survival (days), median (range)	423 (17-2764)	716 (17-2762)	238 (35-2764)	184 (35-1705)	638 (101-2764)
Relapse characteristics					
Time to relapse (days), median (range)	147 (2-1373)	n/a	147 (2-1373)	112 (2-1012)	348 (47-1373)
Post-relapse survival (days), median (range)	59 (1-2180)	n/a	59 (1-2180)	58 (1-1330)	126 (7-2180)

[a]*Risk of experiencing any relapse;* [b]*Risk of isolated bone marrow involvement at time of relapse* versus *no relapse;* [c]*Extramedullary disease at time of relapse with (n=2) or without (n=24) bone marrow involvement;* [d]*High risk cytogenetics defines as complex, 5q-, monosomy 7, 7q-, FLT3 positive;* [e]*Match based on A, B, C and DR loci;* [f]*tacrolimus/methotrexate ± other agents* versus *all others.*

and physical examination as appropriate. In 16 patients these remissions were facilitated by local therapy, which included radiation therapy to all patients with testicular leukemia (n=2), both of whom received therapy to one other extramedullary site (mediastinal mass and central nervous system chloroma); all other patients with central nervous system involvement (n=12) received intrathecal chemotherapy and/or radiation. Two patients with bone chloromas also received radiation therapy prior to HSCT. The two patients with persistent extramedullary disease prior to HSCT had soft tissue chloromas.

Incidence and characteristics of extramedullary relapse

The 5-year cumulative incidence of isolated extramedullary relapse was 9%, while 29% of patients experienced an isolated bone marrow relapse. Less than 1% of patients (n=2) developed simultaneous extramedullary and bone marrow relapse. Extramedullary relapses occurred significantly later than isolated marrow relapses (Figure 1A; median 348 *versus* 112 days, respectively; $P<0.001$). Skin and soft tissue were the most common sites of extramedullary relapse, but relapses in lymph nodes, bone, central nervous system and other sites were also observed; extramedullary relapse in multiple sites was observed in 38% (n=10) of patients (Table 2). Nine extramedullary relapses occurred in patients with a history of extramedullary leukemia prior to HSCT. Post-HSCT extramedullary relapse occurred in prior sites of involvement in five cases (including worsening chloromas in two patients who had active chloromas prior to HSCT), while the remaining four patients experienced new sites of extramedullary disease at the time of relapse. Only two relapses occurred in sites that had received local therapy in addition to systemic treatment prior to HSCT. Five of 24 patients (21%) who initially had isolated extramedullary disease at relapse later developed bone marrow involvement. Conversely, only three of the 73 patients with isolated bone marrow disease at relapse later developed extramedullary disease (4%); in each case the extramedullary site of disease was the central nervous system. Overall, the central nervous system was involved in eight patients: in five cases only the spinal fluid was affected, one case had isolated chloroma, and two cases had both spinal fluid involvement and chloroma.

Risk factors for extramedullary relapse after hematopoietic stem cell transplantation

We first determined hazard ratios (HR) for any type of relapse (extramedullary and/or bone marrow) for each of the individual risk factors (Table 3). Patients with high risk cytogenetics, M4/M5 leukemia according to the French-

Table 2. Location of extramedullary disease at relapse.

Extramedullary site[a]	N. of patients (%)
Skin/soft tissue	20 (77%)
Lymph nodes	6 (23%)
Bone	6 (23%)
Central nervous system	5 (19%)
Pleura	5 (19%)
Visceral organs	4 (15%)
Testicle(s)	1 (4%)

[a]*10/26 (38%) patients presented with extramedullary disease in multiple sites.*

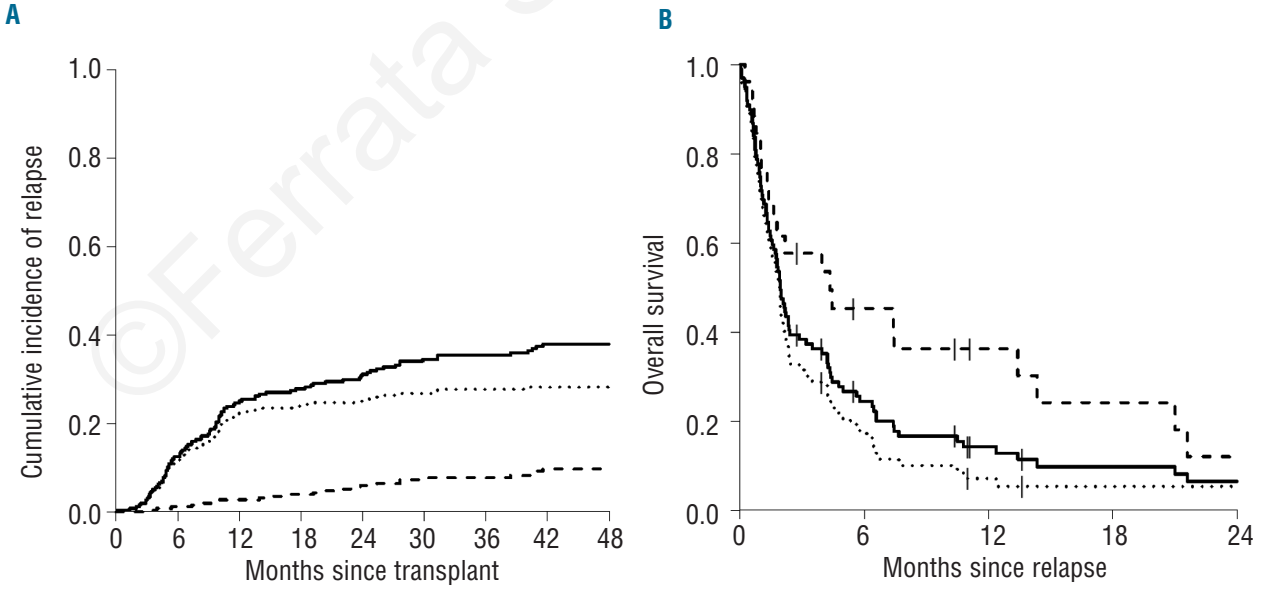

Figure 1. Cumulative incidence of relapse and post-relapse survival. All relapses shown as a solid line, isolated bone marrow relapse as a dotted line, extramedullary ± bone marrow relapse as a dashed line. (A) Cumulative incidence of relapse following HSCT for AML. Any relapse (solid line) – 38% (n=99); isolated bone marrow relapse (dotted line) – 28% (n=73); extramedullary ± bone marrow relapse (dashed line) – 10% (n=26); extramedullary *versus* isolated bone marrow relapse; $P<0.001$. (B) Two-year overall survival following AML relapse post-HSCT. Any relapse (solid line) – 6% (n=6/99); isolated bone marrow relapse (dotted line) – 5% (n=4/73); extramedullary ± bone marrow relapse (dashed line) – 15% (n=4/26). Extramedullary *versus* isolated bone marrow relapse; $P=0.03$.

American-British (FAB) classification, advanced disease status and children were more likely to relapse than patients lacking these risk factors or adults.

We then determined hazard ratios for extramedullary relapse for the same risk factors tested earlier. Thus, we analyzed whether a given risk factor was more or less likely to be present in patients with extramedullary relapse than in those who did not experience relapse. Risk factors for extramedullary relapse are shown in Table 3. Chief among these, a history of extramedullary disease at any time point prior to transplantation (n=31) was predictive of future extramedullary relapse (HR=4.6, $P<0.001$). Patients with extramedullary relapse were significantly more likely to have FAB class M4 or M5 AML (HR=2.5, $P=0.02$), which are known to have a higher frequency of extramedullary disease.[12,15] Advanced disease status at the time of HSCT and high-risk cytogenetics, both well-known risk factors for post-HSCT bone marrow relapse,[16-19] also correlated with an increased risk of extramedullary relapse (HR=2.6, $P=0.02$ and HR=2.9, $P=0.006$, respectively). This finding has not previously been reported. Previously implicated leukemic features predicting post-HSCT extramedullary relapse such as CD56 and T-cell marker expression[11,12,20] were not associated with extramedullary relapse in our population. Additionally, we did not find convincing statistical evidence to suggest that reduced intensity conditioning increased the risk of extramedullary relapse (HR=5.8, $P=0.08$), but there was a trend in that direction. Children were 3.3 times more likely to experience extramedullary relapse than adults ($P=0.006$), although children also had higher incidences of other risk factors including a prior history of extramedullary disease (35% *versus* 8%; $P<0.001$) and FAB M4/M5 leukemia (42% *versus* 30%; $P=0.14$).

The development of acute GVHD was not protective against relapse in either the bone marrow or extramedullary sites. However, chronic GVHD did correlate with a 50% reduction in overall relapse risk. Importantly, the protective effect of chronic GVHD did not extend to extramedullary sites; patients who developed chronic GVHD were as likely to experience extramedullary relapse as they were to never experience relapse. The sites of extramedullary relapse did not differ between patients with chronic GVHD and patients without chronic GVHD, but the number of relapses per site was too few to fully explore the possibility that specific sites, such as the central nervous system, might be more resistant to a chronic GVHD protective effect than others.

Treatment and outcome of extramedullary relapse after hematopoietic stem cell transplantation

Treatment data and outcomes were available for 25 of the 26 patients with extramedullary disease at relapse; four patients elected not to pursue additional antileukemic therapy, all of whom died within 2 months. The remaining 21 patients were treated with radiation to sites of relapse (n=2), systemic chemotherapy only (n=9), or both systemic chemotherapy and radiation to chloromas (n=10). Eight patients also received donor leukocyte infusions (Table 4). Both patients who received only radiation therapy died of progressive disease. Seven of the remaining 19 patients (36%) entered a complete remission, four of whom are still alive. Two of the surviving patients received donor leukocyte infusions. The three patients who entered remission but died did so from either subsequent leukemia recurrence (n=1) or chronic GVHD complications (n=2).

As previously noted, there were three patients whose extramedullary relapse (all in the central nervous system) was first preceded by a post-HSCT isolated bone marrow relapse. None of these patients was in remission from their marrow relapse despite chemotherapy, and, in one case, also post-donor leukocyte infusion GVHD, at the time of their central nervous system relapse. All three patients died from refractory leukemia.

Patients with extramedullary disease at initial relapse survived significantly longer after relapse than those with isolated bone marrow relapse (Figure 1B; median 126 *versus* 58 days, respectively; $P=0.03$), but outcomes were uniformly poor. The overall survival rate after extramedullary

Table 3. Univariate analysis of risk factors for any relapse (n=99) and extramedullary relapse (n=26).

	Any relapse, hazard ratio, (*P*)	Extramedullary relapse, hazard ratio[a], (*P*)
Pre-transplant risk factors		
Age ≤18 years at diagnosis	**1.7 (0.04)**	**3.3 (0.006)**
EM disease prior to transplant	**1.2 (0.6)**	**4.6 (<0.001)**
High risk cytogenetics[b]	**1.6 (0.03)**	**2.9 (0.006)**
FAB M4/M5	**1.6 (0.03)**	**2.5 (0.02)**
T-cell markers	0.8 (0.3)	1.4 (0.4)
CD56 expression	1.3 (0.4)	2.2 (0.08)
Related donor	1.1 (0.5)	0.9 (0.8)
HLA matched donor[c]	1.6 (0.08)	2.7 (0.1)
Gender mismatch	0.9 (0.7)	1.2 (0.6)
Stem cell source (peripheral blood *vs*. other)	0.9 (0.6)	1.0 (1.0)
Disease status CR3+/refractory at HSCT	**2.0 (0.001)**	**2.6 (0.02)**
Transplant risk factors		
TBI in conditioning, n. (%)	0.6 (0.3)	1.3 (0.7)
Busulfan in conditioning, n. (%)	1.6 (0.3)	0.7 (0.6)
Full intensity conditioning, n. (%)	0.8 (0.5)	5.8 (0.08)
Tacrolimus/methotrexate in GVHD prophylaxis[d]	1.2 (0.5)	1.0 (0.9)
Any acute GVHD	1.3 (0.2)	1.4 (0.4)
Skin only	1.2 (0.5)	1.5 (0.4)
Visceral ± skin	1.5 (0.1)	2.2 (0.1)
Chronic GVHD	**0.5 (0.003)**	**1.6 (0.3)**

[a]*Risk of extramedullary (EM) ± marrow disease at the time of relapse* versus *no relapse;* [b]*High risk cytogenetics defined as complex, 5q-, monosomy 7, 7q-, FLT3 positive;* [c]*Match based on A, B, C and DR loci;* [d]*Tacrolimus/methotrexate ± other agents* versus *all others. TBI: total body irradiation; CR3+: third complete remission or beyond.*

Table 4. Treatment and outcomes for patients with extramedullary relapse post-HSCT.

Treatment[a]	N. receiving (%)	N. achieving CR (%)	Median survival (days)
None	4 (15%)	0 (0%)	25 (7-66)
Chemotherapy ± radiotherapy	13 (50%)	4 (31%)	120 (18-2180+)
DLI s/p chemotherapy ± radiotherapy	8 (31%)	3 (38%)	226 (23-824+)

[a]*Treatment data unavailable for one patient who experienced extramedullary relapse. DLI: donor lymphocyte infusion.*

relapse was 30% at 1 year and 12% at 2 years, while the survival rates at the corresponding times after isolated bone marrow relapse were 8% and 5%, respectively.

Discussion

Extramedullary relapse of AML following allogeneic HSCT remains a poorly understood post-HSCT outcome. The incidence of extramedullary relapse in this study (10%) is consistent with previously reported rates over the past 35 years despite many changes in allogeneic HSCT practices.[21,22] Although it is possible that patients with risk factors for extramedullary relapse are currently more likely to undergo allogeneic HSCT than they were in the past, it is more likely that the stable incidence reflects a lack of progress in this scenario. In this series of patients, we confirmed that the increased risk of extramedullary relapse for most previously reported risk factors, including pre-HSCT extramedullary disease, FAB M4/M5 AML, and advanced disease status, also apply to the post-HSCT setting.[10,20] We did not, however, find there was an increased risk associated with CD56 or T-cell marker expression. While not surprising, our finding that patients with advanced disease status or high risk cytogenetics had an excess risk of extramedullary relapse when compared to no relapse is new. The increased risk of extramedullary relapse in children is presumably related to their higher incidence of a history of extramedullary disease and FAB M4/M5 AML. Multivariate analysis would be required to determine whether age alone was an independent risk factor for extramedullary relapse, or whether the effect of age could be explained by other factors that were more common in children, but our sample size did not support such analysis. While the other risk factors we identified are biologically plausible, our findings must be interpreted cautiously given the lack of a multivariate analysis.

A key finding from this study is an improved understanding of the distinctly different pattern of relapse for extramedullary sites compared to the bone marrow. Extramedullary leukemia manifests itself clinically much later after HSCT than do bone marrow relapses. This difference may be partially due to the fact that some extramedullary sites may harbor growing leukemia without symptoms for a prolonged period, but that explanation may not be sufficient to explain the entire 8-month difference in median time to relapse. We did not see a protective effect of acute GVHD against relapse, an observation that differs from that in another recent study of post-HSCT relapse of AML, although protection against extramedullary relapse, specifically, was not found in either study.[23] It is noteworthy that extramedullary sites appear to be resistant to the otherwise protective effect of chronic GVHD for relapse. Taken together, these findings suggest that extramedullary sites may act as sanctuary locations for leukemic cells, thus providing protection from both cytotoxic conditioning regimens and immune surveillance through the graft-*versus*-leukemia effect. It is also possible that the protective effect of chronic GVHD on relapse varies according to site, with the strongest effect on the bone marrow, and variable effects ranging from none to modest at other extramedullary sites. The number of relapses at each site was too few to permit performance of a site-specific analysis.

The poor long-term survival of patients after any type of AML relapse highlights the need for new therapeutic strategies to be developed for these patients. Approaches that are perhaps less dependent on immunotherapeutic aspects may be more efficacious in the setting of extramedullary relapse, given the lack of correlation with chronic GVHD and comparable outcomes between patients receiving chemotherapy alone and those receiving chemotherapy together with donor leukocyte infusions for extramedullary relapse. One such strategy could be the administration of maintenance-like chemotherapy after HSCT in order to provide preventive antileukemic therapy above and beyond that which is provided by the graft-*versus*-leukemia effect. An ideal drug to administer in this fashion would be well tolerated, have a large volume of distribution (i.e. good tissue penetrance), and be able to be administered on a schedule that ensures the presence of killing concentrations when quiescent leukemia cells re-enter the cell cycle. Recent reports on the use of hypomethylating agents as maintenance treatment for high-risk AML following HSCT provide an example of this strategy.[24]

Acknowledgments

The authors would like to thank the clinicians of the University of Michigan Blood and Marrow Transplant program and the University of Michigan clinical research support staff.

Funding

This research was supported by NIH grants 5P30-CA46592, P01-CA039542-23A1, and T32-HL007622.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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