Published in final edited form as:

Leuk Lymphoma. 2013 March ; 54(3): 665–668. doi:10.3109/10428194.2012.720375.

Extramedullary relapse following reduced intensity allogeneic hematopoietic cell transplantation for adult acute myelogenous leukemia

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Keywords

extramedullary; relapse; allogeneic transplantation; AML; acute myelogenous leukemia

Extramedullary relapse following allogeneic hematopoietic transplantation (alloHCT) for acute leukemia was first highlighted as a problem by a survey of European Blood and Marrow Transplantation (EBMT) Registry data in 1996, citing an occurrence rate of 0.65% of surveyed transplants for acute myelogenous leukemia (AML) [1]. The incidence of extramedullary relapse is difficult to determine due to the retrospective nature of the published studies and small sample sizes, but is reported to be between 5 and 12% with [2–8]. A literature review of 112 published cases of AML extramedullary relapse finds a median onset time of 17 months (range 1–121) post-transplant, with sites reported (in order of highest frequency) in skin, breast, bone, testis, serosa, gynecological tract, and bladder [9]. Likely due to the low incidence, published reports differ on whether extramedullary relapse has distinct risk factors and prognosis compared to bone marrow relapse and it is unclear whether there might be differences in conditioning regimens.

To better understand the incidence and predictors of extramedullary (EM) relapse following reduced intensity conditioning (RIC)-alloHCT for AML, we identified and analyzed a consecutive case-series of 246 adult AML patients who underwent RIC-alloHCT from February 2000 through December 2008 at City of Hope from a prospective observational research transplant database. Based on the observation of multiple extramedullary relapses in patients receiving RIC-alloHCT following a fludarabine/melphalan conditioning regimen, we hypothesized that this regimen might have a higher-than-expected incidence of extramedullary relapse. The COH Institutional Review Board approved the use of these data. Pathology review of biopsy specimens was conducted by the COH Hematopathology department to confirm the diagnosis of AML prior to RIC-alloHCT. Disease status at RIC-alloHCT was confirmed by clinical assessment including physical examination, laboratory

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The authors declare no competing financial interests.

evaluation, imaging by CT scans and nuclear imaging, bone marrow biopsies and photo documentation per COH patient care standard operating procedures.

The median age at RIC-alloHCT was 55 years (range: 19–71) with a fairly balanced gender distribution (male=125, 51%; female=121, 49%). There were 108 (44%) matched related donors and 138 (56%) matched unrelated donors. 221 (90%) patients received peripheral blood stem cells. The median time from diagnosis to RIC-alloHCT was 6.4 months (range: 0.5–124.8). Disease status at RIC-alloHCT: 1CR/2CR=137(56%), induction failure=40 (16%), relapse=69 (28%). Nine percent (n=22) of patients had a history of EM relapse prior to RIC-alloHCT. Twenty-eight percent of patients (n=68) received a prior auto (n=50) or allo (n=18) HCT. The majority of patients received fludarabine/melphalan conditioning n=227, 92%. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and mycophenolate mofetil in 111 patients (45%) or tacrolimus and sirolimus in 135 (55%). A total of 205 patients were evaluable for cytogenetics. Based on Southwest Oncology Group criteria [10], 10 patients (4.8%) had favorable, 118 (57.6%) had intermediate and 77 (37.6%) had unfavorable cytogenetics.

The primary endpoint was relapse/progression incidence (RP), defined as time from transplant to recurrence or progression. Cumulative incidence curves were generated for RP in the competing risks setting, given that non-relapse deaths and relapse/progression events were in competition. The cumulative incidence of RP was calculated using the method described by Gooley *et al* [11]; differences between cumulative incidence curves in the presence of a competing risk were tested using the Gray method [12]. The significance of demographic and treatment features was assessed using stratified survival analysis and univariate, multivariable Cox proportional hazards regression analysis [13], or the corresponding hazard analysis for competing risks [14]. The risk factors studied were: prior extramedullary disease (yes, no), prior HCT (yes, no), disease status at the time of RIC-alloHCT (CR, IF/RL/>3CR), cytogenetic risk (favorable/intermediate, unfavorable), age at RIC-alloHCT (<55, ≥55), de novo AML (yes, no), prior radiation (yes, no), aGVHD (None/I, II–IV), and cGVHD (yes, no). All calculations were performed using SAS 9.2 (SAS Institute, Cary, NC) or R (version 2.14.2, <http://www.r-project.org>). General, statistical significance was set at the $p < 0.05$ level; all P values were two-sided. For multivariable Cox regression, factors shown to be significant at the $p < 0.10$ level univariately, were included in the analysis. The data were locked for analysis on October 1st, 2011 (analytical date).

The median follow-up was 61.7 months (range: 24.6–132.9) for surviving patients. At last contact, 87 patients (35%) were alive and 159 (65%) had expired. Initial relapse/progression occurred in the bone marrow (BM) in 81 (32.9%) patients and extramedullary sites (EM) in 18 (7.3%) patients, 5 of whom had concurrent BM+EM relapse/progression. The sites were: brain/CSF-5, breast-3, multiple sites-2, spine-1, liver-1, ascites-1, thigh mass-1, testes-1, bone-1, mediastinum-1, and mesentery-1. In addition, 10 (4%) patients had a second relapse in an EM site. The sites of second or subsequent relapse were: brain/CSF-3, multiple sites-3, spine-1, parietal mass-1, mediastinum-1, and oropharynx-1. Treatment for initial EM relapse/progression included: combined chemo-radiotherapy-8, radiotherapy and/or chemotherapy followed by second alloHCT or DLI-3, chemotherapy only-3, palliative care-3, and radiotherapy only-1, and for subsequent EM relapse, there were combined chemo-radiotherapy-4, radio- and/or chemotherapy followed by second alloHCT or DLI-3, chemotherapy-1, and palliative care-2.

In all analyses, the EM group refers to all 18 patients with EM relapse, including the 5 with concurrent BM relapse, while the BM group refers to the 76 patients with bone marrow relapse and no extramedullary disease. We also performed analyses treating the concurrent

EM/BM relapses separately, but the groups were too small to attain significance, and the results were qualitatively similar. The two-year cumulative incidence of initial EM relapse/progression was 4.9% (95% CI: 2.8–8.5), and for BM relapse was 29.8% (95% CI: 24.5–36.1). Figure 1 shows the cumulative incidence curves for relapse/progression for both EM and BM relapse. Time from RIC-alloHCT to initial EM relapse/progression was 12.2 months (range: 2.8 - 42.9) and time from RIC-alloHCT to initial BM relapse/progression was 6.7 months (range: 0.9–33.3).

Overall survival following transplantation for the entire cohort of 246 patients was 63.0% (95% CI: 59.1–66.7) at 1 year and 50.8% (95% CI: 47.6–53.9) at 2 years. Overall survival after initial EM relapse/progression was 44.4% (95% CI: 34.1–54.3) at 6 months, and after initial BM relapse/progression was 42.1% (95% CI: 37.4–46.7) at 6 months. Median survival after EM relapse was 4.8 months (95% CI: 3.8–8.4) and after BM relapse was 4.6 months (95% CI: 2.6–6.8). There were no significant differences between survival after EM and BM relapse ($p=0.52$). In the EM group, there were 5 patients with concurrent bone marrow involvement and 13 with strictly extramedullary involvement at first relapse. Of the 5 patients with concurrent bone marrow disease, 4 died from disease progression. Of the 13 patients with strictly extramedullary disease at 1st relapse, 9 patients died of disease progression. Of these 9, 6 died due to extramedullary disease and 2 had a subsequent bone marrow relapse before dying. For the last patient, it is unknown whether there was subsequent bone marrow involvement before death.

Using Cox regression modeling we assessed the effect of the risk factors [prior EM disease, prior HCT, disease status at RIC-allo-HCT, cytogenetic risk (unfavorable, others), age at RIC-alloHCT (<55, ≥55), de novo AML (yes, no), prior radiation (yes, no), aGVHD (None/I, II–IV), and cGVHD (yes, no)] on predicting EM relapse/progression. The only factor found to be predictive by univariate analysis was cytogenetic risk (HR: 5.4, 95% CI: 1.8–16.5, $p<0.01$). Patients with poor risk/unfavorable cytogenetics showed a five-fold increase in the risk of EM relapse/progression. Cytogenetics was not a significant risk factor for BM relapse/progression with a hazard ratio of 1.5 (95% CI: 0.9–2.4, $p = 0.09$).

This report specifically characterizes extramedullary relapse of AML post RIC-alloHCT with a uniform fludarabine/melphalan conditioning regimen. Our data show that the rate of EM relapse following RIC-alloHCT for AML of 7.3% (18/246 patients) is intermediate between the 12.3% reported following full-intensity busulfan/cyclophosphamide conditioning for alloHCT [2] and the 5.3% reported following non-myeloablative alloHCT [4]. By univariate analysis, unfavorable cytogenetics was associated with an increased risk of EM relapse, similar to findings in the literature. We did not detect any differences in survival based on bone marrow versus extramedullary relapse, as did some studies reporting that patients with isolated extramedullary relapse have a better prognosis than do patients with systemic relapse [5,8]. In conclusion, reduced-intensity conditioning with fludarabine/melphalan does not appear to be associated with a greater-than-expected risk of EM relapse compared to rates from studies using either full intensity or a mixture of full intensity and reduced intensity allo-HCT. In this study cohort, extramedullary relapse was distinguished from bone marrow relapse only in its later occurrence post- transplantation (12.2 versus 6.7 months) and its association with cytogenetics as a significant risk factor.

Acknowledgments

This work was supported by grant # P01 CA 30206.

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Figure 1. Cumulative Incidence of Relapse/Progression

The cumulative incidence curves for bone marrow relapse/progression (n=76, solid line) and extramedullary relapse/progression (n=18, dashed line) are plotted from the date of transplantation (in years). The 18 extramedullary relapses include 5 patients with concurrent bone marrow relapse. Curves were calculated using non-relapse mortality as a competing risk.

Table 1

Patient, Disease and Treatment Characteristics *

Variable	Total Cohort (n=246)	BM Relapse (n=76)	EM Relapse* (n=18)
Age at Transplant: median years (range)	55 (19 -71)	55 (19–71)	55.5 (24–66)
Donor Type			
Related donor	108 (44%)	36 (47%)	6 (33%)
Unrelated donor	138 (56%)	40 (53%)	12 (67%)
Time from DX to alloHCT: median months (range)	6.4 (0.5–124.8)	6.3 (0.6–59.1)	11.6 (0.6–45.1)
Disease Status at alloHCT			
ICR / 2CR	137 (56%)	35 (46%)	9 (50%)
PR / 1RL / 2RL / 3CR / IF / Untreated	109 (44%)	41 (54%)	9 (50%)
Prior transplant			
Allogeneic	18 (7%)	6 (8%)	1 (6%)
Autologous	50 (20%)	13 (17%)	3 (17%)
Cytogenetic Risk at Diagnosis			
High-risk Unfavorable	77 (31%)	30 (39%)	12 (67%)
Other	169 (69%)	46 (61%)	6 (33%)
Radiation Therapy prior to HCT			
Total Body Irradiation	52 (21%)	15 (18%)	3 (17%)
Breast	12 (4.9%)	3 (4%)	2 (11%)
Other	14 (5.7%)	1 (1%)	1 (6%)
Extramedullary AML prior to HCT	22 (9%)	5 (7%)	2 (11%)
De Novo AML			
Yes	142 (58)	41 (54%)	12 (67%)
No (treatment-related or evolved from MDS)	104 (42)	35 (46%)	6 (33%)
Acute GVHD	160 (65%)	47 (62%)	10 (56%)
Grade I	51	14	1
Grade II	60	20	7
Grade III	26	11	2
Grade IV	23	2	6
Chronic GVHD			
Yes	161 (66%)	40 (53)	12 (67%)
Limited	22	7	2
Extensive	139	33	10
No	55 (22%)	35 (46)	5 (27%)
Died prior to cGVHD evaluation	30 (12%)	1 (1)	1 (6%)

Variable	Total Cohort (n=246)	BM Relapse (n=76)	EM Relapse* (n=18)
Death Events	159 (65%)	70 (92%)	17 (94%)
Cause of Death			
Disease Progression	73 (46%)	59 (84%)	13 (76%)
Disease-Related Therapy	4 (3%)	1 (1%)	0 (0%)
Infection	27 (17%)	4 (6%)	1 (6%)
Other	50 (31%)	4 (6%)	2 (12%)
Unknown	5 (3%)	2 (3%)	1 (6%)

* The EM Relapse category includes the 5 patients with concurrent bone marrow and extramedullary relapse

BM–bone marrow, EM–extramedullary, DX–diagnosis, HCT–hematopoietic cell transplantation, CR–complete remission, PR–partial remission, RL–relapsed, IF–induction failure, AML–acute myelogenous leukemia, MDS–myelodysplastic syndrome, GVHD–graft-versus-host disease, cGVHD–chronic graft-versus-host disease