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Central Nervous System Involvement in Acute Myeloid Leukemia Patients Undergoing Hematopoietic Cell Transplantation

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A B S T R A C T

Knowledge regarding the rate of central nervous system (CNS) involvement and risk factors for its development in acute myeloid leukemia (AML) patients undergoing allogeneic hematopoietic cell transplantation (HCT) are limited. In this study we retrospectively evaluated CNS involvement in 327 patients who underwent myeloablative HCT at our institute in which all patients have cerebrospinal fluid examined by morphology or flow cytometry before HCT. Twenty-two patients (7%) had CNS AML involvement at pre-HCT evaluation. Covariates associated with such involvement were higher WBC at diagnosis, prior CNS or other extramedullary disease, and evidence of systemic disease at pre-HCT evaluation. History of prior CNS disease and disease status at pre-HCT evaluation allowed stratification of patients into 3 risk groups: 35% (20 patients), 16% (51 patients), and 3% (256 patients) rates of pre-HCT CNS involvement. Treatment of pre-HCT CNS disease was uniformly successful regardless of whether cranial irradiation therapy was used. Perhaps as a result, presence of CNS pre-HCT had no independent influence on post-HCT outcome, which was primarily influenced by status of systemic disease at time of HCT.

INTRODUCTION

The exact incidence of central nervous system (CNS) involvement in adults with acute myeloid leukemia (AML) is unknown but is considered uncommon (<5%) [1-3]. Therefore, cerebrospinal fluid (CSF) evaluation is usually performed only in patients with neurological symptoms and, unlike in acute lymphoblastic leukemia, prophylactic therapy is not indicated [4]. Risk factors associated with CNS AML are higher pretreatment levels of lactate dehydrogenase and WBCs, chromosome 16 inversion and chromosome 11 abnormalities, FAB subgroup M4 and M5, and younger age [5,6]. Although high-dose cytarabine, intrathecal chemotherapy, and cranial irradiation are effective treatments, relapse rate is high and CNS involvement considered to be a poor prognostic factor [2,7-9].

Allogeneic hematopoietic cell transplantation (HCT) can be curative in AML [10,11]. However, despite advances in therapy, relapse remains the major cause of post-HCT mortality [12,13]. The incidence of CNS disease before and after transplant and the effect of CNS disease on transplant outcome is uncertain [3]. At our institution all AML patients considered candidates for allogeneic HCT undergo routine CSF examination as part of a pretransplant evaluation, allowing a relatively unbiased look at the incidence of AML in CSF pre-HCT. Therefore, the primary objectives of this study were to assess the rate of CNS involvement in AML patients undergoing HCT, evaluate potential risk factors for CNS disease, and examine the effect of CNS involvement on transplant outcome.

METHODS

Patient Population

We retrospectively evaluated 327 adults (age ≥ 18 years) with AML who underwent myeloablative HCT at the Fred Hutchinson Cancer Research Center between January 2007 and December 2012. Per standard practice at our institution, all patients underwent routine evaluation for CNS AML involvement at the time of pre-HCT evaluation by morphological or multiparameter flow cytometric evaluation of cytospun CSF. AML CNS involvement was defined as unequivocal morphological or immunophenotypic evidence of leukemic blasts in the CSF or in symptomatic patients by abnormal findings on computed tomography or magnetic resonance imaging.

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Table 1
Patient Characteristics

Characteristic	No CNS Involvement at Pre-HCT Evaluation (n = 305)	CNS Involvement at Pre-HCT Evaluation (n = 22)	*P*
Median age at HCT, yr (range)	49 (19-73)	50 (22-69)	.49
Gender			.66
Male	160 (52)	19 (45)	
Female	145 (48)	12 (55)	
Median WBC count at diagnosis, $\times 10^3/\mu L$ (range)	5 (0-800)	34 (2-269)	<.001
Risk group*			.15
Unfavorable	79 (26)	5 (23)	
Favorable	23 (8)	5 (23)	
Intermediate-I	128 (42)	7 (32)	
Intermediate-II	75 (25)	5 (23)	
Prior CNS involvement			<.001
Yes	13 (4)	7 (32)	
No	290 (96)	15 (68)	
Prior EMD (no CNS)			.04
Yes	25 (8)	5 (23)	
No	280 (92)	17 (77)	
Prior HDAC treatment			1.0
Yes	195 (64)	14 (67)	
No	108 (36)	7 (33)	
Disease status at pre-HCT evaluation			.0015
CR no MRD	163 (53)	4 (18)	
CRp/CRi	38 (12)	3 (14)	
CR-MRD	60 (20)	5 (23)	
No CR	44 (14)	10 (45)	
CR status at pre-HCT evaluation			
CR1	185 (61)	3 (14)	
CR2	70 (23)	4 (18)	
CR $\geq$ 3	6 (2)	5 (23)	
No CR	44 (14)	10 (45)	
HCT allotype			.23
HLA matched-related	102 (33)	10 (45)	
HLA matched-unrelated	118 (39)	7 (32)	
HLA mismatched-related	8 (3)	2 (9)	
HLA mismatched-unrelated	55 (18)	3 (14)	
Graft source			.19
Bone marrow	58 (19)	8 (36)	
Peripheral blood	208 (68)	13 (59)	
Cord blood	38 (12)	1 (5)	

HDAC indicates histone deacetylase.
Values are number of cases with percents in parentheses, unless otherwise noted.
* Based on European LeukemiaNet risk classification [4,20].

All patients with evidence of CNS involvement at pre-HCT evaluation were treated by intrathecal/intraventricular chemotherapy (±cranial irradiation) and entered transplant with no evidence of CNS disease. Transplant conditioning regimens included busulfan/cyclophosphamide (n = 84), treosulfan/fludarabine/± low-dose total body irradiation (TBI) (n = 79), busulfan/fludarabine (n = 54), cyclophosphamide/high-dose TBI (n = 37), fludarabine/I^{131} anti-CD45 Ab/± cyclophosphamide (n = 35), cyclophosphamide/fludarabine/high-dose TBI (n = 33), and others (n = 5).

All patients provided informed consent for treatment approved by the institutional review board. Separate institutional approval was obtained to gather data from patient records and databases for this retrospective study.

CSF Evaluation

Cytomorphological evidence of CNS involvement was defined by microscopic counting of myeloblasts in cytospun CSF preparations stained with May-Grunwald-Giemsa. Cytomorphological analysis performed on cytospun preparations is highly specific (>95%) but has a lower sensitivity of approximately 80% [14]. In most cases CSF was also evaluated by multiparametric flow cytometry, which has a diagnostic value more than twice that of cytomorphology [15]. Flow cytometry analysis was performed on a modified 4-laser, 10-color Becton Dickinson LSRII flow cytometer (BD Biosciences, San Jose, CA) as previously described [16].

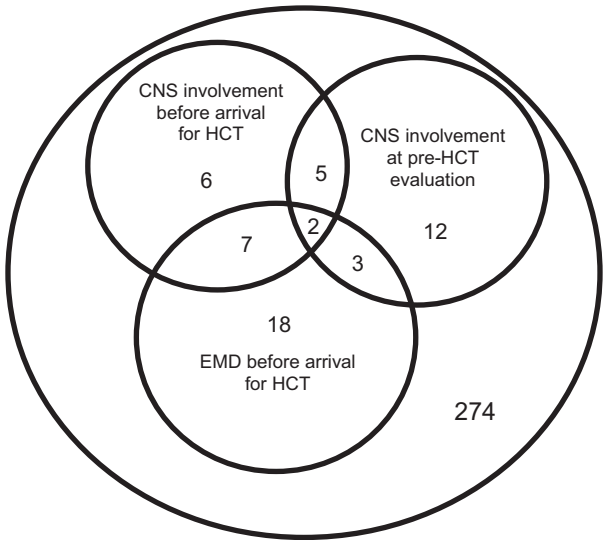

Figure 1. Prior CNS and EMD among 327 AML patients undergoing myeloablative HCT.

Statistical Methods

Wilcoxon rank sum tests were used to compare quantitative variables, and Fisher's exact test was used to compare categorical variables in patients with and without CNS involvement. Overall survival (OS) after transplant was measured from date of transplant to date of death due to any cause, with patients last known to be alive censored at the date of last contact. Relapse-free survival (RFS) after transplant was measured from the date of transplant to the date of first relapse or death from any cause, with patients last known to be alive in complete remission (CR) censored at the date of last contact. Time to relapse after transplant was measured from date of transplant to date of relapses, with deaths in CR considered a competing event. OS and RFS were estimated with the Kaplan-Meier method, and time to relapse was estimated using cumulative incidence curves. Cox regression models were used to assess OS and RFS, and proportional hazards models for the subdistribution of a competing risk were used to assess time to relapse. Multivariable analyses for CNS involvement at time of transplant included history of CNS involvement and other extramedullary disease (EMD), remission status, cytogenetics, prior high-dose cytarabine ($\geq$500 mg/m^2 per dose), and the quantitative covariates WBC count and age. Classification and regression tree analysis was used to define subgroups at differing risk of CNS disease at time of HCT.

RESULTS

Patient Characteristics

We retrospectively evaluated 327 adults with AML who underwent myeloablative HCT. Median age was 49 years (range, 19 to 73). Twenty-eight patients (9%) had favorable karyotype (SWOG criteria), 215 (66%) had intermediate-risk karyotype, and 84 (26%) had unfavorable karyotype at diagnosis; 209 patients had received high-dose cytarabine. At time of CNS evaluation pre-HCT, 167 patients were in CR without minimal residual disease (MRD), 65 had CR with MRD, 41 had CR with incomplete platelet recovery (CRp) or CR with incomplete blood count recovery (CRi), and 54 had overt systemic relapse (>5% blasts in marrow). Twenty patients had a prior history of CNS disease. Median follow-up time among patients censored for OS was 3.1 years (1130 days). Characteristics of patients are presented in Table 1.

Predictors of CNS Relapse

Thirty-five patients (11%) had AML CNS involvement at any time pre-HCT; among them, 22 (7%) had CNS AML