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Allogeneic Hematopoietic Cell Transplantation May Alleviate the Negative Prognostic Impact of Monosomal and Complex Karyotypes on Patients with Acute Myeloid Leukemia

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A B S T R A C T

Monosomal karyotype (MK) and complex karyotype (CK) are well known to be associated with a very poor clinical outcome in patients with acute myeloid leukemia (AML). However, whether or not the prognostic impact of MK and CK remains relevant for patients who have undergone allogeneic hematopoietic cell transplantation (allo-HCT) is still unclear. We retrospectively analyzed the status of MK and CK, as well as other clinical laboratory features, in 148 allo-HCT AML patients at our institution and correlated with their event-free survival (EFS) and overall survival (OS) after transplantation. MK and CK were identified in 14 (9%) and 19 (13%) cases, respectively. On univariate analysis, only age (≥60 years) and WBC count ($\geq 15 \times 10^9$/L) were significant adverse predictors for EFS ($P < .001$ and $P = .017$, respectively) and OS ($P = .002$ and $P = .021$, respectively). MK, CK, and other relevant parameters analyzed did not affect the clinical outcome. Multivariable analysis confirmed that both older age and high WBC count were independent prognostic factors for a shorter OS ($P = .001$ and $P = .003$, respectively) and a shorter EFS ($P < .001$ and $P = .001$, respectively). Our results indicate that neither MK nor CK are high-risk factors in AML patients undergoing allo-HCT.

INTRODUCTION

Currently, many prognostic factors have been identified for acute myeloid leukemia (AML), a hematological malignancy of myeloid stem cells with heterogeneous biology and clinical outcomes. Cytogenetic information has been shown to have high prognostic strength in a patient's response to therapy, their risk of relapse, and their overall survival (OS) [1-4]. Various methods of stratifying cytogenetic risk have been proposed by groups such as the Medical Research Council (MRC), Southwest Oncology Group/Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and Dana-Farber Cancer Institute [1-4]. In all these risk stratifications there has been a consensus that complex karyotype (CK, defined as ≥4 autosomal structural abnormalities by revised MRC criteria or as ≥3 autosomal structural abnormalities by Southwest Oncology Group criteria) results in a poor prognosis [1-4]. Age and WBC count have also long been shown to have prognostic value in AML as well [5-9]. Monosomal karyotype (MK, defined as ≥2 autosomal monosomies or 1 autosomal monosomy with other structural abnormalities) has more recently been shown to be a very strong predictor, stronger than both cytogenetic risk and CK [8,10-14]. Certain immunophenotypic markers, such as CD7, CD11b, CD15, CD34, CD56, and CD117, have also been found to be prognostic in AML [15-28].

However, the research around prognostic factors for AML patients who undergo allogeneic hematopoietic cell transplantation (allo-HCT) is not nearly as extensive. Prognostic factors determined for transplant patients include bone marrow status, donor relatedness, source of stem cells, time between diagnosis and allo-HCT, remission status at time of allo-HCT, and cytogenetic risk, including CK and MK [11,29,30]. Whether or not MK and CK remain significant after allo-HCT is still debatable, with different centers finding contrasting trends [7,31,32]. Here we investigated whether or not MK and CK (following revised MRC criteria) were negative risk factors for AML patients undergoing allo-HCT. In addition, we evaluated the prognostic impact of various clinical laboratory features including patient age, sex, WBC count, cytogenetic risk, and presence of immunophenotypic markers CD7, CD11b, CD15, CD34, CD56, and CD117, while adjusting for time between diagnosis and allo-HCT, remission status at time of allo-HCT, and donor relatedness.

METHODS

Our retrospective study included adult AML patients at the University Health Network, Toronto, Ontario, Canada. The study was approved by the Research Ethics Board of the University Health Network. From our pool of 1740 AML patients, who were first registered at the University Health Network between January 2005 and December 2012, 230 patients received allo-HCT, of which 148 had available cytogenetic information. These 148 transplant patients received their allo-HCT between December 2005 and January 2013. The median time from diagnosis to transplantation was 9.1 months. Patients were stratified by cytogenetic risk based on revised MRC guidelines [1]. Patients with acute promyelocytic leukemia were included and placed under low cytogenetic risk. Patients younger than age 60 years received myeloablative conditioning regimens (cyclophosphamide-total body irradiation [TBI], busulfan-cyclophosphamide, cytarabine+cyclophosphamide+TBI, or fludarabine+4 day dose of busulfan +/− low-dose TBI), whereas patients older than age 60 received nonmyeloablative conditioning regimens (fludarabine+low-dose TBI, fludarabine+2-day dose of busulfan +/− low-dose TBI).

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Only patients in either first complete remission (CR1) or second complete remission (CR2) were transplanted according to the program policy.

Our non-transplant control group consisted of 200 age-matched adult AML patients at the same center who did not receive allo-HCT. Furthermore, the control group was selected only from patients who had survived at least 6 months to account for the fact that every patient in our transplant group had to survive a certain amount of time before they could receive allo-HCT. The choice of 6 months was based on the median time from diagnosis to transplantation for our MK patients. Six months after diagnosis was used as a reference point for the non-transplant group and the date of allo-HCT as our start point for transplant patients.

Karyotype Analysis

Karyotypes were obtained from diagnostic bone marrow samples with standard methods and in accordance with International System for Human Cytogenetic Nomenclature guidelines [33]. A minimum of 20 metaphases were required to have been examined to rule out the presence of clonal chromosomal abnormalities.

Immunophenotypic Analysis

To perform immunophenotypic analysis, bone marrow or peripheral blood samples were prepared and processed using a whole blood lysis technique, followed by multiparameter flow cytometry (FC 500 Flow Cytometer, Beckman Coulter, Miami, FL). Leukemic blasts were selected based on the dim CD45 presence against low side scatter and then analyzed with various combinations of 4 to 5 conjugated antibodies along with an autofluorescent negative control [16]. Only samples that contained 20% or more blasts and 10,000 list mode events recorded at the blast gate were used in the analysis; presence of an antigen was considered positive if it was expressed on at least 20% of the blasts in the sample.

Statistical Analysis

Categorical variables such as gender, age over 60, WBC count $> 15 \times 10^9$/L, cytogenetic risk, CK, MK, time between diagnosis and allo-HCT over 18 months, remission status at time of allo-HCT, donor relatedness, CD7, CD11b, CD115, CD34, CD56, and CD117 were summarized with counts and percentages. Continuous variables, such as follow-up duration, time to relapse, and patient age, were summarized with medians and ranges as necessary. Follow-up duration was based on the last follow-up, starting from the date of allo-HCT. Time to relapse was calculated up to date of relapse, starting from the date of allo-HCT. Patient age was calculated for the age of the patient on the date of their allo-HCT. Endpoints for our non-transplant control group used a date 6 months after diagnosis as a reference point in place of date of transplant.

OS and event-free survival (EFS) were calculated using the Kaplan-Meier product-limit method. Log-rank test was used as a univariate analysis to compare levels of the potential predictive factors. Cox proportional hazards regression was used to assess the joint effect of predictors on OS and EFS that were found to be a potential predictor at the univariate level and/or that are clinically important. A covariate was considered as a potential predictor if the univariate analysis produced $P \leq .20$ [34]. Variables considered clinically important for this study were WBC count, cytogenetic risk, CK, MK, time between diagnosis and allo-HCT over 18 months, patient status at transplant, and donor relatedness. Results were considered significant if $P < .05$. Potential predictors from the univariate were put through a backward stepwise Wald Cox proportional hazards regression until remaining covariates had $P < .10$, after which another Cox proportional hazards regression was done with the significant covariates ($P < .05$) from the backward stepwise Wald analysis, along with the clinically important variables. All P values were 2-sided and pertained to the event hazard ratio rather than comparing survival percentages at given times. Statistical analyses were performed using SPSS v20 (IBM; Armonk, NY).

RESULTS

Patient Characteristics

Patient characteristics and statistical results for the 148 patients in the transplant population group are summarized in Table 1. The median age of the patients at time of transplantation was 51.9 years (range, 24.2 to 70.9). Of the 148 patients, 12 (8%) were good risk, 110 (74%) were intermediate

Table 1
Univariate Analysis and 4-Year Survival for OS and EFS for the Allo-HCT Population (N = 148)

Characteristic	Subcategory	All Patients n (%)	<TSH>OS		<TSH>EFS	
			4-Year Survival (%)	Log Rank *P*	4-Year Survival (%)	Log Rank *P*
Age	<60 yr	108 (73)	53	**.002***	49	**< .001***
	≥60 yr	40 (27)	25		20	
Sex	Male	78 (53)	41	.243	36	.249
	Female	70 (47)	49		46	
WBC count	$<15 \times 10^9$/L	87 (59)	51	**.021***	47	**.017***
	$\geq 15 \times 10^9$/L	61 (41)	36		33	
Cytogenetic risk	Favorable	12 (8)	43	.921	43	.856
	Intermediate	110 (74)	46		41	
	Unfavorable	26 (18)	41		36	
CK	−	137 (93)	45	.642	42	.324
	+	11 (7)	37		26	
MK	−	134 (91)	46	.436	42	**.182**
	+	14 (9)	36		28	
Time between diagnosis and HCT	<18 mo	122 (82)	47	**.105**	43	**.084**
	≥18 mo	26 (18)	33		29	
Status at transplantation	CR1	113 (76)	47	.292	44	**.178**
	CR2	35 (24)	36		30	
Donor	Related	74 (50)	47	.314	43	.277
	Unrelated	74 (50)	42		38	
CD7	−	94 (64)	41	**.199**	37	**.150**
	+	33 (22)	53		53	
CD11b	−	55 (37)	45	.479	45	.321
	+	70 (47)	43		38	
CD15	−	53 (36)	38	.978	36	.890
	+	73 (49)	44		41	
CD34	−	45 (30)	47	.512	42	.666
	+	79 (53)	41		38	
CD56	−	97 (66)	42	.664	40	.829
	+	18 (12)	38		38	
CD117	−	37 (25)	46	.989	38	.696
	+	81 (55)	41		41	

Values in bold indicate $P < .20$. CD indicates cluster of differentiation.
* Univariate significance.