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Original Article

Impact of pre-transplant bone marrow blast percentage on survival in acute myeloid leukemia patients

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Abstract: Background and Objectives: Allogeneic hematopoietic stem cell transplantation (alloHSCT) remains the most effective treatment for most of the patients with acute myeloid leukemia (AML). The aim of this study is to investigate the impact of pre-transplant bone marrow blast cell percentage on transplant outcomes and survival. Materials and Methods: One hundred and twenty-two patients with AML who received an alloHSCT in our HSC transplant center between the years of 2001 and 2018 were evaluated. For the estimation of pre-transplant blast percentage, the highest estimate from bone marrow aspirate (by manual count) and core biopsy (pathologist estimates) were used. Results: Of the 122 patients, 97 (79.5%) patients had pre-transplant BM blast cells <5% and 25 patients had pre-transplant BM blast cells 5%-10%. Sixty-six patients (54%) underwent a MAC regimen whereas 56 (46%) patients received a RIC regimen. Median follow-up for survivors was 21 months (range 4-203). The 5-year OS for patients who had pre-transplant BM blast cells <5% and patients who had pre-transplant BM blast cells 5%-10% were 65% and 18%, respectively (p<0.001). The 5-year disease free survival (DFS) for patients who had pre-transplant BM blast cells <5% and patients who had pre-transplant BM blast cells 5%-10% were 62% and 32%, respectively (p=0.01). Cox regression analysis revealed sex of the patients (p=0.02), ECOG PS of the patients (p=0.006) and developing chronic GVHD (p=0.02) were parameters to predict OS. Cox regression analysis revealed pre-transplant bone marrow blast (%) (p=0.04) as the only parameter to predict DFS. Conclusion: In conclusion, the present study demonstrated that pre-transplant bone marrow blast percentage before alloHSCT is undoubtedly an important prognostic factor for patients with AML. Thus, further studies using more reliable methods to investigate the clinical significance of minimal residual disease at transplant are needed.

Keywords: Acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, pre-transplant bone marrow blast percentage

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) remains the most effective treatment for most of patients with acute myeloid leukemia (AML) [1]. The two major mechanisms by which alloHSCT can cure AML are through the immunologically-based graft versus leukemia (GVL) effect and leukemic cell cytoreduction by the HSCT conditioning regimen [2-4]. The anti-neoplastic potency of these reduced intensity conditioning (RIC) regimens relies primarily on the GVL effect rather than ablating all residual leukemic disease [5]. Disease status at the time of alloHSCT, older age, cytogenetic risk status, and development of graft-versus-host disease (GVHD) are considered to be important prognostic factors in patients undergoing alloHSCT for AML [6-8]. Regarding pre-transplant disease status, patients who underwent transplantation during the first complete remission had a long-term survival benefit for intermediate- and high-risk AML, with a diseases free survival (DFS) rate of more than 45% [3]. The aim of this study was to investigate the impact of pre-transplant bone marrow blast cell percentage on survival and transplant outcomes. We retrospectively examined the blast counts from aspirates before alloHSCT as well as conditioning regimens to deter-

mine their relationships with transplant outcomes in AML patients, as well as the relationship to disease and patient characteristics.

Materials and methods

Study design and data collection

This study has been performed in a retrospective manner. One hundred and twenty-two patients with AML who received an alloHSCT in our HSC transplant center at Hacettepe University Hospital between the years of 2001 and 2018 were evaluated. The induction therapies, IA (idarubicin and Ara-C) based strategies with conventional idarubicin (13 mg/m^2 IV push on each of first 3 days of treatment) and Ara-C doses (100 mg/m^2 daily as a continuous infusion for 7 days) were performed in all patients [10]. The patients received HiDAC 3 g/m^2 every 12 h on days 1, 3 and 5. Demographic data of the patients, transplantation data and post-transplantation updates were obtained from the hospital database. Antiviral prophylaxis against Herpes simplex and Varicella zoster, and prophylaxis against *Pneumocystis jirovecii* continued at least six months following alloHSCT. For estimation of pre-transplant blast percentage, the highest estimate from the bone marrow aspirate (by manual count) and core biopsy (pathologist estimates) were used. Due to existing protocols of the hospitals of Hacettepe Medical School, all of the studied patients had given informed consents at the time of hospitalization, before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care. DFS was defined as time from ASCT to disease progression or death due to any cause. OS was defined as time from ASCT to death due to any cause. Patients who were alive and free of disease were censored at their last follow-up visit.

Patients and disease characteristics

In this study, the patients included were as follows: age >18 years at the time of diagnosis, receiving their first ASCT, and patients who received consolidation chemotherapy courses after induction chemotherapy. HiDAC consolidation chemotherapy began 4 weeks after CR if patients had a performance status of 0, 1 or 2 (ECOG scale) [11], no persisting infection, adequate renal (creatinine <2 mg/dL) and hepatic (serum alkaline phosphatase <2× normal, transaminases <4× normal, and bilirubin <2 mg/dL) function. Stem cell sources included matched related donors (MRDs) (HLA identical sibling), donor peripheral blood stem cells were mobilized with granulocyte colony-stimulating factor. Peripheral blood stem cells were used in all transplantation. Sixty-six patients received a myeloablative conditioning (MAC) regimen and 56 patients received a RIC regimen. The indications for selecting the RIC regimen were as follows: inadequate organ funcion (defined as serum transaminase levels >3× upper limit of normal reference value, total bilirubin >2 mg/dL; creatinine clearance <60 mL/min; left ventricular ejection fraction <50%); serious fungal infection before transplantation (lung, liver or other sites), Eastern Cooperative Oncology Group (ECOG) performance status ≥2) and the patient's refusal of MAC regimen.

Statistical analyses

Demographic characteristics were presented using proportions and medians (minimum-maximum) for categorical and continuous variables, respectively. Statistical comparisons were made using the Chi-square test for categorical data. The Student's t-test (for 2 independent samples) or the Kruskal Wallis test (for more than 2 independent samples) were used for comparisons of continuous numerical data. Survival analyses were made using the Kaplan-Meier test. The Log rank test was applied to compare survival data. Overall survival was calculated from the date of diagnosis to death for any reason. Surviving patients were counted on the date of the final follow-up examination. Disease-free survival was calculated from the date of complete remission to relapse or death in remission. Patients surviving in remission were counted on the date of the final follow-up examination. Univariate analyses of the differences in OS and DFS were applied using log-rank tests. Univariate comparisons with a p value <0.20 were included in the multivariate analyses in which $p<0.05$ was considered statistically significant. Cox regression analysis was used to study the simultaneous effect of selected variables on survival. Values of p <0.05 were accepted as statistically significant. The statistical analyses were performed using SPSS v17 software (SPSS Inc, Chicago, IL, USA).

Table 1. Baseline characteristics of AML patients

Parameters	Blasts in pre-transplant BM <5%	Blasts pre-transplant BM 5%-10%	p
N	97 (79.5%)	25 (20.5%)	
Gender (male/female) (%)	51/46 (52.6%/47.4%)	19/6 (76%/24%)	0.03
The median age at transplantation (range), years	39 (18-68)	46 (22-66)	0.06
Conditioning regimen			0.83
RIC	52 (53.6%)	14 (56%)	
MAC	45 (46.4%)	11 (44%)	
ECOG Performance Status			0.50
0	3 (3.1%)	2 (8%)	
1	73 (75.3%)	17 (68%)	
2	21 (21.6%)	6 (24%)	
Diseases risk index			0.03
Low	0	0	
Intermediate	73 (75.3%)	14 (56%)	
High	17 (17.5%)	9 (36%)	
Very high	0	1 (4%)	
Missing	7 (7.2%)	1 (4%)	
Cytogenetic risk group			0.90
Favorable	0	0	
Intermediate	72 (74.2%)	18 (72%)	
Adverse	16 (16.5%)	5 (20%)	
Missing	9 (9.3%)	2 (8%)	
Cell counts in the transplant (CD34+)	7.6 (2.1-24.8)	7.9 (1.7-23.7)	0.88
Neutrophil engraftment (range) days	11 (8-19)	11 (10-15)	0.30
Platelet engraftment (range) days	12 (8-19)	13 (7-40)	0.01
Acute GVHD	13 (13.4%)	3 (12.0%)	0.85
Chronic GVHD	28 (28.9%)	5 (20.0%)	0.37
Relapse (%)	30 (30.9%)	11 (44.0%)	0.21
Mortality (%)	28 (28.9%)	14 (56.0%)	0.01
Non-relapse mortality	8 (8.2%)	2 (8%)	0.96

Abbreviations: BM: Bone marrow; ECOG PS: ECOG Performance Status; GVHD: Graft versus host diseases; Reduced intensity conditioning; MAC: Myeloablative conditioning; n: Number of the patients.

Results

Patients characteristics

A total of 122 patients were entered into the study between 2001 and 2018. Patient characteristics are summarized in **Table 1**. There were 70 males and 52 females with a median age of 40 (range, 18-68) years at the time of transplantation. The number of patients classified with Eastern Cooperative Oncology Group performance status 0, 1 and 2 were 5, 90 and 27 respectively (11). Karyotype analyses were available for 111 patients: 90 patients were in the intermediate-risk group and 21 patients were in the adverse-risk group, according to the European Leukemia Net classification (12). Forty one patients (42.3%) who had pre-transplant BM blast cell <5% and 8 (32.0%) patients who had pre-transplant BM blast cell 5%-10% developed GvHD. GvHD incidence was similar between the two groups after transplantation (p=0.35). Mortality was statistically different between the two groups. Mortality rate was higher in patients who had pre-transplant BM blast cells of 5%-10% in comparison to pre-transplant BM blast cells of <5% (p=0.01). The median time to neutrophil engraftment was 11 days (range 8-19) in the pre-transplant BM blast cells <5% group and 11 days (range 10-15) in the pre-transplant BM blast cells 5%-10% group (p=0.30). The median time to

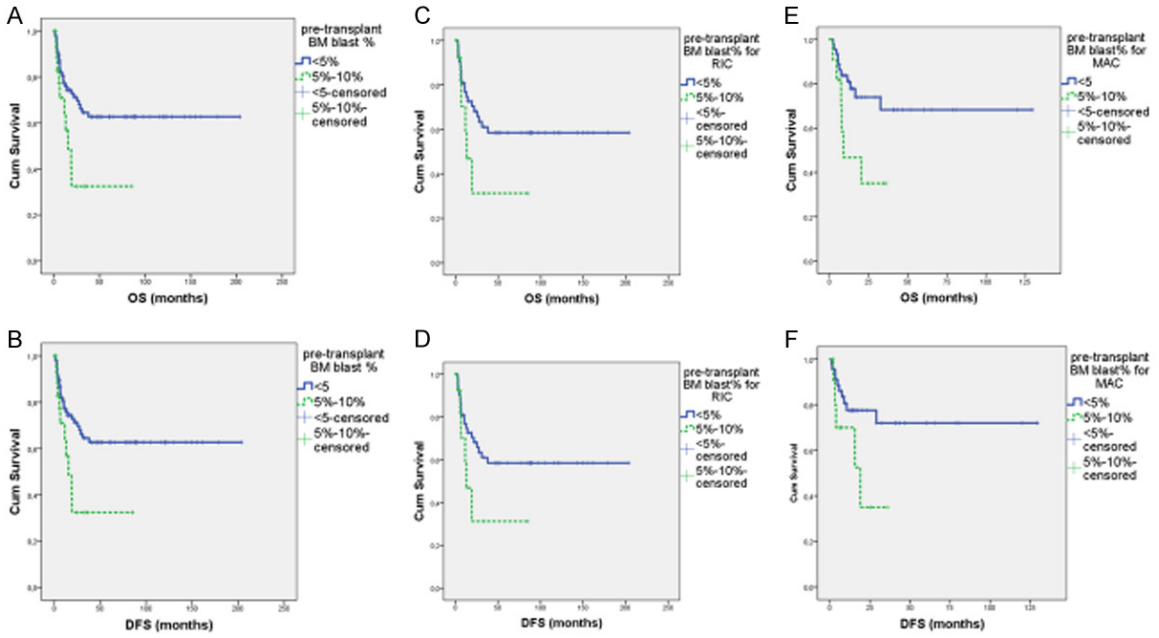

Figure 1. Overall and disease free survival according to pre-transplant bone marrow blast percentage for all patients (A, B), for RIC patients (C, D) and for MAC patients (E, F).

platelet engraftment was 12 days (range 8-19) in the pre-transplant BM blast cells <5% group and 13 days (range 7-40) in the pre-transplant BM blast cells 5%-10% group (p=0.01).

Overall outcomes

Of the 122 patients, 97 (79.5%) patients had pre-transplant BM blast cells of <5% and 25 patients had pre-transplant BM blast cells of 5%-10%. Sixty-six patients (54%) underwent a MAC regimen whereas 56 (46%) patients received a RIC regimen. Median follow-up for survivors was 21 months (range 4-203).

The 3-year overall survival (OS) for patients who had pre-transplant BM blast cells of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 71% and 37%, respectively. The 5-year OS for patients who had pre-transplant BM blast cells of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 65% and 18%, respectively (p<0.001) (**Figure 1A**).

The 3-year disease free survival (DFS) for patients who had pre-transplant BM blast cells of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 64% and 32%, respectively. The 5-year disease free survival (DFS) for patients who had pre-transplant BM blast cell of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 62% and 32%, respectively (p=0.01) (**Figure 1B**).

The 3-year OS for patients who had pre-transplant BM blast cells of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 73% and 39%, respectively, (p=0.003), for the RIC regimen (**Figure 1C**). The 3-year DFS for patients who had pre-transplant BM blast cells of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 61% and 31%, respectively (p=0.10) for the RIC regimen (**Figure 1D**).

The 3-year OS for patients who had pre-transplant BM blast cells of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 73% and 35%, respectively (p=0.03), for the MAC regimen (**Figure 1E**). The 3-year DFS for patients who had pre-transplant BM blast cells of <5% and patients who had pre-transplant BM blast cells of 5%-10% were 72% and 35%, respectively (p=0.05), for the MAC regimen (**Figure 1F**).

Cox regression analyses

In univariate analyses, the factors that affected OS were sex of the patients (male) (p=0.03), ECOG PS of the patients (p=0.06), developing

Table 2. Univariate and Multivariate Analyses (Cox model) of Overall Survival and Disease Free Survival (Note: Univariate comparisons with a *P* value <0.20 were included in multivariate analyses in which statistical significance threshold was accepted as P<0.05)

	Univariate analyses			Multivariate analyses		
Parameters for OS	Hazard ratio	95% confidence interval	*p* value	Hazard ratio	95% confidence interval	*p* value
Age (years)	1.006	0.975-1.038	0.69			
Sex (male/female)	0.497	0.258-0.956	0.03	2.304	1.141-4.653	0.02
Cytogenetic	1.261	0.849-1.874	0.25			
ECOG PS	2.015	0.947-4.260	0.06	2.517	1.299-4.877	0.006
Conditioning Regimen	0.152	0.534-2.484	0.71			
Pre-transplant bone marrow blast (%)	3.215	1.675-6.171	<0.001	1.933	0.929-4.022	0.07
Acute GVHD	0.637	0.257-1.577	0.32			
Chronic GVHD	1.891	0.901-3.970	0.09	0.413	0.194-0.878	0.02
Diseases risk index	1.360	0.919-2.013	0.12	1.259	0.869-1.825	0.22
Parameters for DFS						
Age (years)	1.008	0.985-1.032	0.49			
Sex (male/female)	1.205	0.647-2.244	0.55			
Cytogenetic	1.305	0.880-1.934	0.18	1.391	0.702-2.755	0.34
ECOG PS	1.536	0.814-2.900	0.18	1.287	0.658-2.515	0.46
Conditioning regimen	0.843	0.445-1.595	0.59			
Pre-transplant bone marrow blast (%)	2.336	1.160-4.706	0.01	2.124	1.000-4.512	0.05
Acute GVHD	1.592	0.566-4.478	0.37			
Chronic GVHD	0.885	0.451-1.737	0.72			
Diseases risk index	1.355	0.905-2.028	0.14	1.145	0.634-2.070	0.65

Abbreviations: DFS: Disease-free survival; ECOG PS: ECOG Performance Status; GVHD: Graft versus host diseases; OS: overall survival.

chronic GVHD (p=0.09), disease risk index (p=0.12) and pre-transplant bone marrow blast (%) (p<0.001) as shown in **Table 2**. Cox regression analysis revealed sex of the patients (p=0.02), ECOG PS of the patients (p=0.006) and developing chronic GVHD (p=0.02) were parameters to predict OS.

In univariate analyses the factors that affected DFS were cytogenetics of the patients (p=0.18), ECOG PS of the patients (p=0.18), disease risk index (p=0.14) and pre-transplant bone marrow blast (%) (p=0.01). Cox regression analysis revealed pre-transplant bone marrow blast (%) (p=0.04) as the only parameter to predict DFS.

Discussion

The impact of disease load on long-term survival outcome after alloHSCT has been researched by many studies, usually by comparing the outcome of AML patients transplanted in CR with that of patients transplanted in relapse [13, 14]. Previous studies regarding the impact of marrow blasts on transplant outcomes were based on hematological CR, which requires <5% blasts in a BM aspirate [6, 15, 16]. Our main aim was to evaluate the prognostic impact of the pre-transplant bone marrow blast cell percentage on transplant outcomes in patients who underwent alloHSCT for AML. In the present study, we also evaluated the patients according to the conditioning regimen used, namely RIC and MAC.

Kebriaei et al. showed that of the 60 AML patients and 8 myelodysplastic syndrome patients who underwent alloHSCT, the percentage of blasts in the BM was associated with poor OS (p=0.002), for each 10% increase in blasts [17]. Another study also reported the advantage of a low BM blast percentage at transplantation in 36 AML patients receiving alloHSCT. However, the level of 25% blasts was used as the cutoff in their study [18]. In our analyses, the outcomes were better with blast counts lower than 5%, compared with blast counts of 5-10%. At our institution, patients with AML are

routinely advanced to MAC regimen except if significant comorbidities are present. In patients otherwise unsuitable to undergo fully ablative alloHSCT, the presence of pre-transplant >5% blast, although sensed as indicator of increased disease recurrence after transplantation, typically had no role in the decision of MAC vs RIC conditioning. Both for RIC and MAC regimen, the pre-transplant BM blast cell <5% group was associated with better OS than the pre-transplant BM blast cells 5%-10% group. DFS was better in the pre-transplant BM blast cell <5% group than the pre-transplant BM blast cells 5%-10% group, but this difference was not statistically significant when patients were stratified according to conditioning with RIC and MAC. In this study relapse rate was similar between the two groups (p=0.21). A previous study from Oyekunle et al. showed that ≤20% bone marrow blasts was significantly associated with better OS and DFS in 44 patients with refractory AML who underwent alloHSCT with MAC regimen [16]. In another study, pre-transplant variables were evaluated in 59 MDS patients receiving alloHSCT. Patients with fewer blasts at the time of transplant had a decreased rate of relapse compared to those with excess blasts [19].

Our study had a few limitations. First, this study was retrospective. Second, the number of non-CR patients was limited. Third, traditional morphological examination of marrow was used for detection of pre-transplant bone marrow blast percentage rather than minimal residual disease (MRD). To accomplish the limitation of traditional assessment of morphological CR, the real-time quantitative polymerase chain reaction (RQ-PCR) method was applied to detect MRD. Monitoring of MRD in AML by RQ-PCR and flow cytometric detection of abnormal immunophenotypes combined with the status of morphological CR has been widely used recently. Thus, enhancing our study using more reliable methods to investigate the clinical significance of residual disease at transplant are needed. In conclusion, the present study demonstrated that achieving a complete remission before alloHSCT is undoubtedly an important prognostic factor for patients with AML. Taken together, the data suggests that further cytoreductive therapy may be necessary prior to transplant in patients with high levels of circulating leukemic blasts, in an effort to increase survival, despite potential added toxicity from additional chemotherapy

Disclosure of conflict of interest

None.

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