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Research paper

Effect of absolute monocyte count post-transplant on the outcome of patients with acute myeloid leukemia undergoing myeloablative allogeneic hematopoietic stem cell transplant with busulfan and cyclophosphamide conditioning

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ABSTRACT

Peripheral monocytes have recently been evaluated as a prognostic factor in different types of hematological malignancies. This study assessed the prognostic value of absolute monocyte count (AMC) post-transplant on the clinical outcomes of 59 patients with acute myeloid leukemia (AML) who had undergone myeloablative conditioning (MAC) allogeneic hematopoietic stem cell transplant (allo-HSCT) with busulfan and cyclophosphamide (Bu/Cy). Kaplan-Meier analysis showed that patients with a high AMC ($\geq 0.57 \times 10^9$/L) on post-transplant day (PTD) 15 had a significantly worse overall survival (OS) compared to patients with a low AMC ($< 0.57 \times 10^9$/L) on PTD 15 (P = .0049). Univariate Cox proportional hazard analyses revealed that only high AMC on PTD 15 was a poor prognostic factor for OS (P = .008) and post-relapse survival (P = .030). We conclude that AMC $\geq 0.57 \times 10^9$/L on PTD 15 is associated with more deaths in patients with AML who have undergone MAC allo-HSCT with Bu/Cy.

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of malignant hematological neoplasms characterized by uncontrolled rapid proliferation of myeloblasts. It is an aggressive leukemia that can be rapidly fatal without treatment [1,2]. Despite improvements in chemotherapy and supportive care, as well as the availability of hematopoietic stem cell transplantation (HSCT) and the development of molecular target therapies during the last two decades, the long-term survival of patients with AML remains poor, as the majority of cases relapse or are refractory to treatment [3,4]. An accurate prognostic assessment is essential to support better clinical management and improve the outcome of patients with AML. Peripheral monocytes, which reflect the tumor microenvironment, have been evaluated as a prognostic factor for various types of hematological malignancies, including diffuse large B-cell lymphoma (DLBCL) [5,6], multiple myeloma [7], follicular lymphoma [8], adult T-cell leukemia/lymphoma [9], chronic lymphocytic leukemia [10], and Hodgkin's Lymphoma [11,12]. In a previous study, we revealed that the absolute monocyte count (AMC) at the time of diagnosis, which provides additional prognostic information independently of conventional factors related to patient clinical characteristics or tumor biological features, was a novel prognostic marker for AML [13].

Furthermore, initial studies have been performed on the impact of AMC post-transplant on the outcomes of allogeneic hematopoietic stem cell transplantation (allo-HCST) for hematological malignancies. A previous study revealed a negative impact of low AMC by post-transplant day (PTD) 100 on overall survival (OS) in patients with myeloid and lymphoid malignancies who had undergone reduced-intensity conditioning (RIC) allo-HSCT with fludarabine and melphalan [14]. Another study found that AMC $> 0.3 \times 10^9$/L on PTDs 30 and 100 is independently associated with improved survival of patients with acute leukemia who have undergone myeloablative conditioning (MAC) allo-HSCT, the majority of which receive a total body irradiation (TBI)-based conditioning regimen [15]. However, these previous studies were complicated by the heterogeneous nature of their study populations regarding disease diagnosis, limiting conclusions specific to AML. In addition, chemotherapy-based conditioning rather than TBI-based

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Table 1
Patients and transplant characteristics by the groups according to AMC at day 15 post-transplant.

Characteristic	Total (n = 59) (%)	AMC at day 15 $< 0.57 \times 10^9$/L (N = 37; 63%)	AMC at day 15 $\geq 0.57 \times 10^9$/L (N = 22; 37%)	P-value
Age, year, median (range)	37 (6–64)	33 (10–64)	39.5 (6–50)	0.9437
0–20	6 (10)	2 (5)	4 (18)	0.133
21–40	30 (51)	22 (60)	8 (36)	
41–63	23 (39)	13 (35)	10 (46)	
Gender				
Male	32 (54)	22 (59)	10 (45)	0.296
Famale	27 (46)	15 (41)	12 (55)	
Donor type				
HLA-matched related	32 (54)	16 (43)	16 (73)	0.082
HLA-matched unrelated	20 (34)	16 (43)	4 (18)	
HLA-haploidentical related	7 (12)	5 (14)	2 (9)	
Disease status at transplant				
CR1	48 (81)	28 (76)	20 (91)	0.146
CR2+	11 (19)	9 (24)	2 (9)	
Number of $CD34^+$ cells $\times 10^6$/kg infused, median (range)	5.19 (1.09−15.3)	5.18 (1.09−12.6)	5.2 (1.5–15.3)	0.5712
Days to ANC 500, median (range)	12 (8–18)	12 (9–18)	12 (8–14)	0.0717
Days to platelet 20000, median (range)	12 (7–20)	13 (7–20)	11 (7–15)	0.0108
Grade of acute GVHD				
0–1	55 (93)	33 (89)	22 (100)	0.110
2–4	4 (7)	4 (11)	0 (0)	
CMV reactivation				
Yes	28 (47)	15 (41)	13 (59)	0.168
No	31 (53)	22 (59)	9 (41)	
Development of chronic GVHD				
Yes	27 (46)	16 (43)	11 (50)	0.614
No	32 (54)	21 (57)	11 (50)	
Relapse				
Yes	12 (20)	6 (16)	6 (27)	0.308
No	47 (80)	31 (84)	16 (73)	
Cause of death				
Relapse-related	10 (17)	4 (11)	6 (27)	0.764
Nonrelapse-related	9 (15)	3 (8)	6 (27)	
Cytogenetic risk				
Favorable	9 (15)	6 (16)	3 (14)	0.795
Intermediate	34 (58)	21 (57)	13 (59)	
Unfavorable	5 (8)	4 (11)	1 (5)	
No data	11 (19)	6 (16)	5 (23)	

AMC, absolute monocyte count; CR, complete remission; ANC, absolute netrophil count; GVHD; graft-versus-host disease; CMV, cytomegalovirus.

conditioning for allo-HSCT is increasingly being used in patients with AML, and a review of a large database showed that in combination with cyclophosphamide, intravenous busulfan (Bu/Cy) is associated with better leukemia-free survival and OS than TBI (Cy/TBI) in patients with AML who have undergone MAC allo-HSCT [16]. Thus, studies focusing on chemotherapy-based MAC for allo-HSCT are needed. In this study, we examined the association between AMC post-transplant and survival in patients with AML who had undergone MAC allo-HSCT with Bu/Cy.

2. Patients and methods

2.1. Patients and transplant procedures

Fifty-nine consecutive patients with AML in remission who received HSCT using HLA-matched related (MRD), unrelated (MUD), or haploidentical related (HID) donors from January 2010 to December 2016 at the First Affiliated Hospital of Wenzhou Medical University, China, were enrolled in this study. There were 28 patients that were also included in our previous work [13]. All patients received grafts derived from peripheral blood (PB), with the exception of patients who had undergone HID transplantation who received bone marrow-derived grafts.

The conditioning regimen consisted of cyclophosphamide (60 mg/kg/day) administered intravenously on days −7 to −6, and busulfan (3.2 mg/kg/day) administered intravenously on days −5 to −2. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A combined with methotrexate for patients who had undergone MRD transplantation or mycophenolate mofetil for patients who had undergone MUD or HID transplantation. *In vivo* T-cell depletion using antithymocyte globulin was added for patients who had undergone MUD or HID transplantation. Relapses diagnosed after HSCT were treated with chemotherapy, with or without a subsequent therapeutic donor lymphocyte infusion (DLI), according to donor availability.

2.2. Data

Data were retrospectively collected from the electronic patient records of the hospital. AMC was collected from the complete blood count (CBC) on days 15, 30, 60 and 100 post-HSCT. The value for the AMC was determined either by the hematology automatic analyzer Sysmex XE-2100 (Sysmex, Kobe, Japan) or manual differential (in cases flagged for abnormal values). Cytogenetic risk at diagnosis was characterized as favorable, intermediate, and unfavorable risk according to the NCCN guidelines [17]. Acute and chronic GVHD were diagnosed using established criteria [18,19].

This retrospective study was approved by the Institutional Review Board (IRB) at the First Affiliated Hospital of Wenzhou Medical University. The requirement for patient informed consent was waived by the IRB due to the retrospective nature of this study, but patient confidentiality was protected.

2.3. Statistical analysis

Categorical variables were compared using Fisher's exact test or the