Original Study

Prognostic Prediction Model for Second Allogeneic Stem-Cell Transplantation in Patients With Relapsed Acute Myeloid Leukemia: Single-Center Report

Sung-Soo Park,[1,2] Hee-Je Kim,[1,2] Kyoung Il Min,[1] Gi June Min,[1,2] Young-Woo Jeon,[1,2] Jae-Ho Yoon,[1,2] Seung-Ah Yahng,[4] Seung-Hwan Shin,[3] Sung-Eun Lee,[1,2] Byung-Sik Cho,[1,2] Ki-Seong Eom,[1,2] Yoo-Jin Kim,[1,2] Seok Lee,[1,2] Chang-Ki Min,[1,2] Seok-Goo Cho,[1] Dong-Wook Kim,[1,2] Jong Wook Lee,[1] Woo-Sung Min[1]

Abstract

Prognostic factors of second allogeneic stem-cell transplantation (allo-SCT2) in 78 patients with relapsed acute myeloid leukemia after first transplantation were explored. Factors included poor cytogenetic risk at diagnosis, circulating blast ≥ 20% at relapse, duration from first transplantation to relapse of < 9 months, and failure to achieve morpohologic complete remission after allo-SCT2. Prognostic model derived from those factors might contribute to appropriate decision making for allo-SCT2.

Purpose: To identify factors affecting survival outcomes and to develop a prognostic model for second allogeneic stem-cell transplantation (allo-SCT2) for relapsed acute myeloid leukemia (AML) after the first autologous or allogeneic stem-cell transplantation. **Patients and Methods:** Seventy-eight consecutive adult AML patients who received allo-SCT2 were analyzed in this retrospective study. **Results:** The 4-year overall survival (OS) rate was 28.7%. In multivariate analysis, poor cytogenetic risk at diagnosis, circulating blast $\geq$ 20% at relapse, duration from first transplantation to relapse $<$ 9 months, and failure to achieve morphologic complete remission after allo-SCT2 were factors associated with poor OS. A prognostic model was developed with the following score system: intermediate and poor cytogenetic risk at diagnosis (0.5 and 1 point), peripheral blast $\geq$ 20% at relapse (1 point), duration from the first transplantation to relapse $<$ 9 months (1 point), and failure to achieve morphologic complete remission after allo-SCT2 (1 point). The model identified 2 subgroups according to the 4-year OS rate: 51.3% in the low-risk group (score $<$ 2) and 2.8% in the high-risk group (score $\geq$ 2) ($P < .001$). **Conclusion:** This prognostic model might be useful to make an appropriate decision for allo-SCT2 in relapsed AML after the first autologous or allogeneic stem-cell transplantation.

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Introduction

Treatment outcome for patients with acute myeloid leukemia (AML) has improved substantially over the past decade. After stem-cell transplantation (SCT), about 30% to 60% of patients experience long-term survival. Unfortunately, disease relapse is the most common cause of treatment failure. It occurs in 20% to 70%

[1]Catholic Blood and Marrow Transplantation Center, Seoul St Mary's Hospital
[2]Leukemia Research Institute, College of Medicine
[3]Yeoido St Mary's Hospital, College of Medicine
[4]Incheon St Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea

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Address for correspondence: Hee-Je Kim, MD, PhD, Department of Hematology, Leukemia Research Institute, Catholic Blood and Marrow Transplantation Center, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpodaero, Seocho-gu, Seoul 06591, Korea
Fax: 82-2-599-3589; e-mail contact: cumckim@catholic.ac.kr

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of patients after SCT for AML. The prognosis of such patients after active treatment is poor, with a median survival of 3 to 4 months.[1-5]

Few therapeutic options are available for patients with relapsed AML after a first autologous or allogeneic SCT (SCT1). National Comprehensive Cancer Network (NCCN) guidelines suggest clinical trial, chemotherapy followed by allogeneic hematopoietic cell transplantation, or best supportive care as treatment strategies, according to patient age.[6] Other studies have suggested that donor lymphocyte infusion (DLI) or epigenetic modifier could be included as treatment strategies for relapsed AML after SCT1.[7] However, no consensus has been reached regarding the optimal treatment strategy for patients with relapsed AML after SCT1.

In numerous reports, patients receiving intensive chemotherapy (IC) supplemented with second allogeneic SCT (allo-SCT2) have better survival than those who receive supportive care alone.[8-13] Compared to treatment strategy of a clinical trial, allo-SCT2 is more easily applied. It also has the theoretical advantage of being able to result in durable remission. Contrary to its theoretical advantage, allo-SCT2 is of no benefit for most patients. Therefore, this approach requires further study. Nevertheless, in terms of accessibility, as well as its being the only treatment option that can induce durable remission, screening for the eligibility of allo-SCT2 is the first step in establishing a suitable treatment strategy for individual patient. However, there is a lack of research on indications for allo-SCT2 through prognostic prediction models.

The objective of this study was therefore to identify factors affecting survival outcomes of allo-SCT2 and to develop a prognostic model using these identified factors to predict survival of patients with relapsed AML as candidates for allo-SCT2. Our results could be used to make appropriate decisions for allo-SCT2 in AML relapse after SCT1.

Patients and Methods

Patients

We retrospectively analyzed data from 78 consecutive patients diagnosed with AML who received allo-SCT2 after IC for disease relapse after SCT1 at our center between August 2002 and August 2016. The types of SCT1 (autologous or allogeneic) in these patients were decided by our center's strategy as follows.[14] We first considered allogeneic SCT1 as a consolidative treatment for patients who experienced first complete remission (CR). When donors were not available or when patients refused allogeneic SCT1, we recommended autologous SCT1 as a consolidative treatment. All donors for SCT2 were allogeneic and were different from those for SCT1. This study was approved by the institutional review board of the Catholic Medical Center (KC17RESE0407) in accordance with the principles of the Declaration of Helsinki.

Definition and Variables for Developing Prognostic Prediction Model

All outcomes were measured from the date of the second transplantation. Relapse was defined as the reappearance of leukemic blasts in the peripheral blood (PB) or $\geq$ 5% infiltration of a representative bone marrow (BM) smear. In univariate and multivariate analyses, circulating blast at diagnosis (or relapse) was defined as the highest of measured value between the time of diagnosis (or relapse) and induction (or reinduction) chemotherapy. Response to treatment, including morphologic or cytogenetic CR and CR with incomplete blood count recovery (CRi), was defined according to the revised recommendation by the International Working Group for AML.[15] Hematopoietic cell transplantation comorbidity index was assessed according to the method outlined by Sorror et al.[16] Acute and chronic graft-versus-host disease (GVHD) were diagnosed and graded according to consensus criteria.[17,18]

Cytogenetic and Molecular Studies

All cytogenetic and molecular studies were performed using serial follow-up BM samples at the time of initial diagnosis, at relapse after SCT1, and before allo-SCT2. Karyotyping with at least 20 metaphases was performed from BM cells using the GTG banding method after 24 or 48 hours of unsynchronized culture. The International System for Cytogenetic Nomenclature[19] and NCCN[6] were used as guidelines for cytogenetic risk stratification. *FLT3* internal tandem duplication (ITD) mutation was detected using multiplex allele-specific RT-PCR (Absolute *FLT3 TKD*/ITD RT-PCR kit; BioSewoom, Seoul, Korea) based on methods described previously.[20] The *c-kit* mutation was detected by melting curve analysis by RT-PCR (Real-Q C-KIT screening kit and D816muta-ID kit; BioSewoom) to detect *c-kit* mutation located at Asp816 (D816) and Asn822 (N822K) in exon 17, as described in our previous reports.[21,22]

Remission Strategy for Relapsed AML After First Transplantation

All patients received IC for relapsed AML after SCT1. The major regimen of reinduction chemotherapy consisted of 5 days of fludarabine (30 mg/m^2 per day), cytarabine (1 g/m^2 per day), mitoxantrone (10 mg/m^2 per day), and granulocyte-colony stimulating factor (300 μg per day; combination of mitoxantrone, cytarabine, fludarabine, and granulocyte-colony stimulating factor [FLANG] regimen,[23] n = 61). For patients who had morbidity and expected to be intolerable with the FLANG regimen, we administered a MEC regimen (mitoxantrone 10 mg/m^2 on days 1-4, etoposide 100 mg/m^2 on days 5-7, and cytarabine 1.0 g/m^2 bid on days 1-4, n = 7) or other regimens (n = 9). In patients with proven extramedullary manifestation at relapse, local radiotherapy and/or intrathecal chemotherapy were administered followed by IC on the basis of our strategy for AML with extramedullary involvement.[24] After reinduction chemotherapy, all patients who had an available donor were treated with allo-SCT2 as a postremission or salvage treatment. For patients without a suitable donor at the time of postreinduction chemotherapy, consolidating or additional salvage induction chemotherapy with or without DLI was administered according to the response of the first reinduction chemotherapy or before allo-SCT2. Because all the patients who underwent DLI for relapsed AML after allo-SCT1 at our center died of secondary relapse or of DLI-related death (especially GVHD) without an opportunity to receive allo-SCT2, our study cohort did not include these patients.

Second Transplantation Procedure, GVHD Prophylaxis, and Supportive Care

According to our center's treatment strategy, the second transplantation was allogeneic regardless of whether the SCT1 was autologous or allogeneic. Of note, all patients who underwent allogeneic SCT1 received allo-SCT2 using different donors from those in SCT1. Patients received either a myeloablating conditioning (MAC)

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