Biol Blood Marrow Transplant 21 (2015) 1632–1640

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Clinical Research: Alternate Donors

Effect of Granulocyte Colony–Stimulating Factor–Combined Conditioning in Cord Blood Transplantation for Myelodysplastic Syndrome and Secondary Acute Myeloid Leukemia: A Retrospective Study in Japan

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Article history:
Received 15 April 2015
Accepted 10 May 2015

Key Words:
Granulocyte colony–stimulating factor
Conditioning regimen
Cord blood transplantation
Myelodysplastic syndrome
Secondary acute myeloid leukemia

A B S T R A C T

Granulocyte colony–stimulating factor (G-CSF) increases the susceptibility of dormant malignant or nonmalignant hematopoietic cells to cytarabine arabinoside (Ara-C) through the induction of cell cycle entry. Therefore, G-CSF–combined conditioning before allogeneic stem cell transplantation might positively contribute to decreased incidences of relapse and graft failure without having to increase the dose of cytotoxic drugs. We conducted a retrospective nationwide study of 336 adult patients with myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (sAML) after single-unit cord blood transplantation (CBT) who underwent 4 different kinds of conditioning regimens: total body irradiation (TBI) $\geq$ 8 Gy + Ara-C/G-CSF + cyclophosphamide (CY) (n = 65), TBI $\geq$ 8 Gy + Ara-C + CY (n = 119), TBI $\geq$ 8 Gy + other (n = 104), or TBI < 8 Gy or non-TBI (n = 48). The TBI $\geq$ 8 Gy + Ara-C/G-CSF + CY regimen showed significantly higher incidence of neutrophil engraftment (hazard ratio, 1.52; 95% confidence interval [CI], 1.10 to 2.08; $P = .009$) and lower overall mortality (hazard ratio, .46; 95% CI, .26 to .82; $P = .008$) rates compared with those without a G-CSF regimen. This retrospective study shows that the

Financial disclosure: See Acknowledgments on page 1639.

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http://dx.doi.org/10.1016/j.bbmt.2015.05.009
1083-8791/

G-CSF–combined conditioning regimen provides better engraftment and survival results in CBT for adults with MDS and sAML.

INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) provides the only chance for long-term survival for patients with myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (sAML) arisen from MDS [1,2]. Cord blood from an unrelated donor has been considered an acceptable alternative graft source in allo-SCT for patients without a human leukocyte antigen (HLA)–compatible related or unrelated donor [3-8]. Although intensified conditioning regimens have been used to decrease the incidence of relapse in high-risk patients who received allo-SCT using adult donors [9-12], whether the use of an intensified conditioning regimen might overcome the higher incidence of graft failure after cord blood transplantation (CBT) remains unclear.

The administration of granulocyte colony–stimulating factor (G-CSF) increases the susceptibility of leukemia cells to the cell cycle–specific agent cytarabine in vitro [13]. Although the priming effect of G-CSF during induction chemotherapy for AML is controversial [14], several studies have reported that the concomitant use of G-CSF and cytarabine arabinoside (Ara-C) during induction chemotherapy led to significantly better survival for patients with newly diagnosed AML [15-17]. Furthermore, the administration of G-CSF before irradiation enhanced engraftment of donor cells in a mouse bone marrow transplantation model [18,19]. Therefore, G-CSF–combined conditioning might contribute to decreased incidences of relapse and graft failure without increasing the dose of cytotoxic drugs.

We previously reported that the addition of G-CSF–combined Ara-C to a total body irradiation (TBI) and cyclophosphamide (CY) conditioning regimen led to a significantly higher incidence of neutrophil engraftment and significantly better survival in CBT in de novo AML [20]. The conditioning regimen originally consisted of Ara-C (total dose 12 g/m^2; 3 g/m^2 every 12 hours for 2 days) with 5 μg/kg G-CSF (lenograstim) from 12 hours before the first dose of cytarabine to the end of the cytarabine dosing, and TBI 12 Gy and CY (total dose 120 mg/kg), which has been described previously [5,6]. However, there has been no comparative study of the transplantation outcomes for MDS and sAML after CBT following a conditioning regimen with or without G-CSF. Therefore, to determine the role of a G-CSF combination in a conditioning regimen before CBT in MDS and sAML patients, we conducted a retrospective nationwide study of 336 adult patients with MDS and sAML in Japan.

PATIENTS AND METHODS

Study Design and Data Collection

The clinical data were provided by the Transplant Registry Unified Management Program (TRUMP) of the Japan Society of Hematopoietic Cell Transplantation [21]. This retrospective study included patients who ranged from 16 to 55 years of age at the time of CBT, who had MDS or sAML, who received single-unit CBT without a prior transplantation history, and who underwent a myeloablative conditioning regimen before CBT. The diagnosis of AML or MDS was made according to the French-American-British classification. We defined *sAML* as AML arisen from MDS. Patients with a diagnosis of chronic myelomonocytic leukemia were excluded from this study. CBTs were performed between July 1998 and December 2012 in Japan. The institutional review board of the Institute of Medical Science, University of Tokyo, approved this study. This study was conducted in accordance with the Declaration of Helsinki.

Endpoints and Definitions

The study endpoints were neutrophil and platelet engraftment, transplantation-related mortality (TRM), relapse, disease-free survival (DFS), and overall survival (OS). *Neutrophil engraftment* was defined as being achieved on the first of 3 consecutive days during which the absolute neutrophil count was at least .5 $\times$ 10^9/L. *Platelet engraftment* was defined as being achieved on the first of 3 consecutive days when the platelet count was higher than 20 $\times$ 10^9/L without transfusion support. *TRM* was defined as death during remission. Relapse was defined as evidence of disease in the peripheral blood, bone marrow, or extramedullary sites. Patients who never achieved remission after CBT were considered to have had a relapse on day 1. The *DFS* (inverse of treatment failure) was defined as the time from the date of CBT to the date of relapse, death in continuous complete remission, or last contact. The *OS* (inverse of overall mortality) was defined as the time from the date of CBT to the date of death or last contact.

The myeloablative conditioning regimen was defined according to the Center for International Blood and Marrow Transplant Research criteria [22]. The conditioning regimen was categorized as 1 of 4 different myeloablative regimens: TBI $\geq$ 8 Gy + Ara-C/G-CSF + CY, TBI $\geq$ 8 Gy + Ara-C + CY, TBI $\geq$ 8 Gy + other, or TBI $<$ 8 Gy or non-TBI. Cytogenetic risk was classified according to the International Prognostic Scoring System criteria [23], although we were unable to use the International Prognostic Scoring System components at diagnosis because of insufficient data in the TRUMP. Because HLA-DR mismatches were previously evaluated at the low-resolution level at cord blood unit selection in Japan [24], data regarding HLA-DRB1 allele information were not fully available in the TRUMP. Therefore, the number of HLA disparities was defined as a low-resolution for HLA-A, -B, and -DR in the graft-versus-host direction. All patients were administered G-CSF after CBT to shorten the duration of neutropenia.

Statistical Analysis

The baseline patient and transplantation characteristics were compared using the chi-square test or Fisher's exact test for categorical variables. The probabilities of DFS and OS were estimated according to the Kaplan-Meier method and the groups were compared using the log-rank test. The probabilities of neutrophil and platelet engraftment, TRM, and relapse were estimated based on a cumulative incidence method to accommodate competing risks. A multivariate analysis was performed with a Cox proportional hazard model adjusted for the DFS and OS, and a Fine and Gray proportional hazards model was used for the other analyses. The following variables were considered: conditioning regimen, age ($<$45 versus $\geq$45 years), recipients' cytomegalovirus serostatus (positive versus negative), the etiology of MDS (de novo versus secondary), cytogenetic risk at diagnosis (favorable versus intermediate versus poor), prior chemotherapy before CBT (no versus yes), the interval from diagnosis to CBT ($<$6 months versus $\geq$6 months), the status of French-American-British classification at CBT (refractory anemia/refractory anemia with ringed sideroblasts versus refractory anemia with excess blasts versus refractory anemia with excess blasts–transformed versus sAML), bone marrow blasts at CBT ($<$5% versus $\geq$5%), cord blood nucleated cell count ($<$2.5 $\times$ 10^7/kg versus $\geq$2.5 $\times$ 10^7/kg), cord blood CD34$^+$ cell count ($<$1 $\times$ 10^5/kg versus $\geq$1 $\times$ 10^5/kg), graft-versus-host disease prophylaxis (cyclosporine-based versus tacrolimus-based), HLA disparities (0 versus 1 versus 2 versus $\geq$3), donor-recipient ABO compatibility (match versus mismatch), and year of CBT (1998 to 2006 versus 2007 to 2012). In this study, the TBI $\geq$ 8 Gy + Ara-C + CY group was considered the reference group according to multivariate analyses, because the main purpose of this study was to evaluate the additional effects of G-CSF in a TBI $\geq$ 8 Gy + Ara-C + CY conditioning regimen. Final model variables were confirmed with a backward selection procedure at the level of significance of $P = .05$. All P values were 2 sided. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for the R 3.0.2 software program (R Foundation for Statistical Computing, Vienna, Austria) [25].

RESULTS

Characteristics of Patients and Grafts

The characteristics of the patients and cord blood units are shown in Table 1. Three hundred thirty-six patients (199