Modified Busulfan and Cyclophosphamide Conditioning Regimen for Allogeneic Hematopoietic Stem Cell Transplantation in the Treatment of Patients With Hematologic Malignancies

X.F. Zhao[a], X.F. Mao[b], D.M. Wan[c,*], and W. Liu[a,*]

[a]Department of Hematology and Oncology, Children's Hospital of Zhengzhou, Zhengzhou, China; [b]Department of Internal Medicine, The No.Three People's Hospital of Henan, Henan, China and [c]Department of Hematology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

ABSTRACT

Objective. We aim to evaluate the clinical efficacy of a modified busulfan and cyclophosphamide (BU/CY) conditioning regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the treatment of hematologic malignancies.

Methods. A total of 45 patients with hematologic malignancies were treated using stem cell transplantation between March 2007 and June 2012. All the patients received a modified BU/CY conditioning regimen before transplantation. The outcomes of the patients were followed up including mortality, survival, relapse, and complications.

Results. The median of follow-up duration was 527 days. All the patients who received modified BU/CY conditioning regimen achieved hematopoietic recovery successfully. Among the patients, 24 were survived without complications, 5 had relapsed hematologic malignancies, and 16 died. The median time to leucocyte engraftment was 14 days and to platelet engraftment was 12 days. Acute graft-versus-host disease (aGVHD; grades I-IV) occurred in 15 patients (30%). The cumulative incidence of grades I aGVHD was 22.2% (10 patients), grades II was 6.7% (3 patients), and grades III-IV was 4.4% (2 patients). Among 40 appreciable patients, 8 (20%) developed chronic GVHD. The incidence rate of hemorrhagic cystitis and veno-occlusive disease were 15.5% and 2.2%, respectively.

Conclusions. The modified BU/CY conditioning regimen for allo-HSCT is effective and safe for the treatment of hematologic malignancies.

HEMATOPOIETIC malignancy was divided into 12 classes by the World Health Organization in 2008, such as acute myeloid leukemia, malignant lymphoma, myelodysplastic syndrome, and leukemia. Currently, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become the most effective method for the treatment of hematologic malignancies, especially for younger patients [1]. Approximately half of the patients achieve excellent disease control when undergoing transplantation during the early phases of the disease, with transplantation-related deaths accounting for 20% to 30% of those caused by therapy failures [2].

Recently, the busulfan and cyclophosphamide (BU/CY) conditioning regimen has become more common for use along with HSCT in patients who have hematologic malignancies [3]. Although the BU/CY conditioning regimen has a remarkably enhanced success rate of implantation, there are several complications, such as acute graft-versus-host disease (aGVHD, with an incidence of 30% to 80%) [4–7]. Experts all over the world are trying their best to modify it [8–11]. It has been shown that risk of relapse reduced and veno-occlusive disease (VOD) morbidity

*Address correspondence to Dingming Wan, Department of Hematology, the First Affiliated Hospital of Zhengzhou University, No.1 Construction of the East Road, Zhengzhou 450000, China. E-mail: dingmingwan@hotmail.com; and Wei Liu, Department of Hematology and Oncology, Children's hospital of Zhengzhou, No.255 GangDu Street, Zhengzhou 450000, China. E-mail: xyxf03@126.com

0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2014.02.023

Table 1. Basic Characters of Patients and Donors

Characteristics	No.
Patients	
No. of patients	45
Age (years; range; median)	6–49 (29.58)
Gender (male/female)	26/19
Disease type	
Chronic granulocytic leukemia	12
Acute myeloid leukemia	
M1	1
M2	12
M4	1
M5	2
Acute lymphoblastic leukemia*	14
High-risk myelodysplastic syndromes	3
Donors	
No. of donors	45
Age (years; range; median)	15–57 (36.8)
Gender (male/female)	16/29
Gender match	
Male to female	10
Female to male	6
Male to male	25
Female to female	4
Source of stem cells	
Marrow	1
Peripheral blood	26
Marrow + peripheral blood	18
ABO-matched	
ABO-compatibility	31
Donor-patient incompatibility	7
Patient-donor incompatibility	3
ABO-incompatibility	4

increased in the conditioning regimen of BU (1 mg/kg) combined with CY (50 mg/kg) every 6 hours for 4 days [12]. In the following studies, duration of CY is reduced and the mortality of transplantation is decreased [13]. On basis of this, BU (1 mg/kg) combined with cytarabine (Ara-C), lomustine and hydroxyurea has the efficacy appropriate to total body irradiation which results in better effect for treating patients who have interstitial pneumonia [14]. However, long-term efficacy and safety of modified BU/CY has not been fully elucidated.

In this study, 45 patients with hematologic malignancies received a modified BU/CY conditioning regimen in our hospital from March 2007 to June 2012. Long-term follow-up examinations were performed to assess the efficacy and safety of the modified regimen. We anticipate that the modified BU/CY regimen may be a preferred treatment for patients who have hematologic malignancies.

SUBJECTS AND METHODS

Subjects and Donors

A total of 45 patients (26 male, 19 female), aged from 6 to 49 years (median, 29.58 years), were enrolled in the First Affiliated Hospital of Zhengzhou University from March 2007 to June 2012 (Table 1). All included patients and donors were informed about the treatment and signed an informed consent form.

Human leukocyte antigen-A (HLA-A), HLA-B, and HLA-DR1 typing were performed at the allele level using high-resolution techniques. All donors and patients were fully HLA-matched and HLA-identical siblings. The source of stem cells was peripheral blood and marrow stem cell transplants in 18 patients, peripheral blood stem cell transplants in 26 patients, and marrow stem cell transplants in 1 patients. A total of 31 cases were ABO-compatible, 7 cases were donor-patient incompatible, 3 cases were patient-donor incompatible, and 4 cases were ABO-incompatible (Table 1).

Conditioning Regimen

All the patients received the conditioning regimen which was modified by previous description [15]. Hydroxyurea (HU, 40 mg/kg, by mouth) was administered every 12 hours on day −10, Ara-C (1–1.5 g/m^2/day, intravenous drip) on day −9, BU (1 mg/kg, by mouth) every 6 hours on days −8 to −6, Cy (1.8 g/m^2/d, intravenous drip) on days −5 to −4, BCNU (250 mg/m^2/d, intravenous drip) on day −3. The urine was hydrated and alkalized on days −2 to −1.

Mobilization, Collection, and Transplantation of Allogeneic Hematopoietic Cells

All donors received granulocyte colony-stimulating factor (rhG-GSF) at a dose of 5 μg/kg/d i.h. on the beginning of day −5. Peripheral blood hematopoietic stem cells were collected using the COBE Spectra. The number of hematopoietic stem cells was determined by flow cytometric analysis. The median of mononuclear cells was 5.68 (2.3∼10.7) × 10^8 per kg, and the median of CD34 cells was 5.84 (1.3∼14) × 10^6 per kg. If the median of CD34 cells was less than 2 × 10^6 cells per kg, a second apheresis was performed on the same day. Fresh hematopoietic donor cells should be transplanted as soon as possible or stored in liquid nitrogen.

GVHD Prophylaxis

All transplant recipients received cyclosporine (CsA) and methotrexate (MTX) in combination with mycophenolate mofetil. CsA (3 mg/kg/day, intravenous drip) was administered continuously for 24 hours on day −1. The dose was reduced on day +50 and stopped on day +180, targeting the serum levels between 200 and 400 ng/mL. Mycophenolate mofetil (1 g/d, by mouth) was given on day −1 to +50. MTX (15 mg/m^2, 10 mg/m^2, 10 mg/m^2) was given on day +1, +3, +6, respectively. Descriptions of the administration were shown in Fig 1.

Supportive Care

Patients received comprehensive medical examination to eliminate the infection in oral cavity, antrum auris, nasal meatus, crissum, and respiratory tract before transplantation. Then, patients received a medicated bath with chlorhexidine (1:2000) and were housed in a laminar flow clean room for the pretransplantation preconditioning. According to the results routine examination of the blood, patients received red blood cells and platelet transfusions with γ-ray irradiation of 25 Gy. Granulocyte colony-stimulating factor was administered to the patients at a dose of 300 μg/d or 150 μg/d until the number of leucocytes was >3.5 × 10^9 per liter or neutrophil granulocytes were ≥1.5 × 10^9 per liter. Patients received supportive care to stop vomiting, protect liver, and provide nutrition. Mesna was used as a prophylactic medication against hemorrhagic cystitis (HC) at a double dose of CU. PGE1 or Compound Danshen injections were administered to prevent VOD. Phenytoin (PHT, 0.1 g