Biol Blood Marrow Transplant 19 (2013) 247–254

Impact of the Direction of HLA Mismatch on Transplantation Outcomes in Single Unrelated Cord Blood Transplantation

Junya Kanda [1], Yoshiko Atsuta [2], Atsushi Wake [3], Tatsuo Ichinohe [4], Minoko Takanashi [5], Yasuo Morishima [6], Shuichi Taniguchi [3], Satoshi Takahashi [7], Hiroyasu Ogawa [8], Kazuteru Ohashi [9], Yuju Ohno [10], Nobuyuki Aotsuka [11], Yasushi Onishi [12], Koji Kato [13], Tokiko Nagamura-Inoue [14], Yoshinobu Kanda [1,*], on behalf of the HLA Working Group of the Japan Society for Hematopoietic Cell Transplantation

[1] *Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan*
[2] *Department of Hematopoietic Stem Cell Transplantation, Data Management/Biostatistics, Nagoya University School of Medicine, Nagoya, Japan*
[3] *Department of Hematology, Toranomon Hospital, Tokyo, Japan*
[4] *Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan*
[5] *Japanese Red Cross Kanto-Koshinetsu Block Blood Center, Tokyo, Japan*
[6] *Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan*
[7] *Department of Molecular Therapy, Advanced Clinical Research Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan*
[8] *Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan*
[9] *Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan*
[10] *Department of Internal Medicine, Kitakyushu Municipal Medical Center, Kitakyushu, Japan*
[11] *Department of Hematology and Oncology, Japanese Red Cross Narita Hospital, Narita, Japan*
[12] *Department of Hematology and Rheumatology, Tohoku University Hospital, Sendai, Japan*
[13] *Division of Hematology Oncology, Children's Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan*
[14] *Department of Cell Processing and Transfusion, Research Hospital, Institute of Medical Science, University of Tokyo, Tokyo, Japan*

Article history:
Received 22 August 2012
Accepted 22 September 2012

Key Words:
HLA incompatibility
Graft-versus-host direction
Host-versus-graft direction
Overall survival
Nonrelapse mortality

A B S T R A C T

The impact of the direction of HLA mismatch (MM) on outcome in unrelated cord blood (UCB) transplantation has not yet been clarified. We conducted a retrospective study using national registry data on 2977 patients who underwent transplantation using a single UCB for leukemia or myelodysplastic syndrome. HLA matching was assessed by serologic data for HLA-A, -B, and -DR loci. The median age of the recipients at transplantation was 41 years (range, 0-82 years), and 2300 recipients (77%) were age ≥16 years. The 2-year overall survival rate was 0.46. The presence of MM only in the graft-versus-host direction or only in the host-versus-graft direction was not associated with overall mortality (hazard ratio [HR], 0.88; $P = .317$ and HR, 0.95; $P = .670$, respectively) compared with 1 bidirectional MM. This finding was consistent in both the child and adult cohorts. The presence of MM only in the graft-versus-host direction was associated with a lower incidence of nonrelapse mortality (HR, 0.65; $P = .040$), significant only in the child cohort. No MM category was associated with relapse. Our findings suggest that the direction of HLA MM does not have a significant impact on overall survival after UCB transplantation.

INTRODUCTION

Unrelated cord blood (UCB) has emerged as a promising alternative source of hematopoietic stem cells for adult and pediatric allogeneic hematopoietic cell transplantation [1-4], and the use of UCB transplantation (UCBT) has been rapidly increasing, particularly in the United States, Europe, and Japan. One advantage of using UCB as a hematopoietic stem cell source is that UCBT requires less stringent HLA matching compared with bone marrow or peripheral blood stem cell transplantation, making it easier to find candidate UCB units in UCB banks. One or 2 antigen/allele mismatches (MMs) in the HLA-A, -B, and -DR loci between a UCB unit and recipient are acceptable without ex vivo T cell depletion methods, and the clinical outcome of transplantation using a 0-2 antigen/allele-mismatched UCB unit was almost comparable to that from an HLA allele-matched unrelated donor [1-3].

Although the number of HLA MMs between a UCB unit and a recipient is usually counted without considering the MM direction, the effect of the immune reaction caused by HLA MM differs according to whether the MM is in the graft-versus-host (GVH) or host-versus-graft (HVG) direction. A mismatched antigen in the GVH direction can be a major target for donor T cells and can cause graft-versus-host disease (GVHD), whereas a mismatched antigen in the HVG direction can be a major target for the remaining recipient T cells and can lead to graft rejection. In related transplantation, the presence of HLA MMs in the GVH direction is associated with a higher incidence of GVHD, whereas the

Financial disclosure: See Acknowledgments on page 254.

* Correspondence and reprint requests: Yoshinobu Kanda, MD, Division of Hematology, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama City, Saitama 330-8503, Japan.
E-mail address: ycanda-tky@umin.ac.jp (Y. Kanda).

1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2012.09.017

presence of HLA MMs in the HVG direction is associated with a higher incidence of rejection [5-7]. Therefore, from a biological perspective, the impact of HLA MM should be discussed separately according to the direction of MM. However, because most patients have an equal number of MMs in the GVH and HVG directions (bidirectional MM), studying an adequate number of patients to evaluate an MM imbalance in the GVH and HVG directions has proven difficult.

The few studies that have evaluated the impact of the HLA MM direction on UCBT outcome have reported inconsistent results [8-10]. Matsuno et al. [8] reported that an HLA MM in the GVH direction was associated with lower incidence of neutrophil engraftment. In contrast, Stevens et al. [9] showed that UCBT with an MM only in the GVH direction was associated with a lower incidence of nonrelapse mortality (NRM) and overall mortality compared with UCBT with an 1 bidirectional MM, whereas UCBT with an MM only in the HVG direction was associated with a lower incidence of neutrophil engraftment and a higher incidence of relapse.

To clarify the significance of the direction of HLA MM on transplantation outcomes, we conducted a retrospective study using national registry data in 2977 patients who underwent a single UCBT.

METHODS

Data Collection

Data for 2987 patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), and chronic myelogenous leukemia (CML) who underwent a first transplantation using a single UCB unit between January 1, 1998, and December 31, 2009, were obtained from the Transplant Registry Unified Management Program (TRUMP) [11], in which all UCBTs are registered through the Japan Cord Blood Bank Network (JCBBN), a national network of all 11 cord blood banks in Japan. Ten patients lacking data on survival status or survival date were excluded. A total of 2977 patients met the criteria for study inclusion. The study design was approved by the TRUMP Data Management Committee and the Institutional Review Board of Saitama Medical Center, Jichi Medical University, where this study was organized.

Histocompatibility

Histocompatibility data for the HLA-A, -B, and -DR loci were obtained from reports collected from the institution at which the transplantation was performed or cord blood banks. HLA typing methods have been described previously [12]. To reflect current practice in Japan, HLA matching was assessed by serologic data for HLA-A, -B, and -DR loci. A secondary analysis using antigen level data for HLA-A, -B and available allele level data for HLA-DRB1 was also performed to compare our data with previously published data from the United States and Europe. HLA-DRB1 allele information was available in 84% of patients (2498 of 2977). Among these patients, 62% had the same number of MMs at HLA-DRB1 loci at either the antigen or allele level. An HLA MM in the GVH direction was defined as when the recipient's antigens or alleles were not shared by the donor, and an MM in the HVG direction was defined as when the donor's antigens or alleles were not shared by the recipient.

Endpoints

The primary study endpoint was overall survival (OS). Other endpoints assessed were relapse, NRM, neutrophil and platelet engraftment, grade II-IV or III-IV acute GVHD, and chronic GVHD. Neutrophil recovery was defined as an absolute neutrophil count exceeding 0.5×10^9/L for 3 consecutive days after UCBT. Platelet recovery was defined as an absolute platelet count exceeding 50×10^9/L without platelet transfusion. The physicians who performed transplantation at each center diagnosed and graded acute and chronic GVHD according to traditional criteria [13,14]. The incidence of acute GVHD was evaluated in patients who engrafted, and that of chronic GVHD was evaluated in patients who engrafted and survived for more than 100 days.

Statistical Analysis

The probability of OS was estimated according to the Kaplan–Meier method and the groups were compared using the log-rank test. The probabilities of relapse, NRM, neutrophil and platelet engraftment, and acute and chronic GVHD were estimated based on cumulative incidence curves [15]. Competing events were death without relapse for relapse, relapse for NRM, death without engraftment for neutrophil and platelet engraftment, and death or relapse without GVHD for acute and chronic GVHD. The groups were compared using Gray's test [16]. The Cox proportional hazards model was used to evaluate the effect of confounding variables on OS, and the Fine and Gray proportional hazards model was used for the other endpoints [17]. Based on the report by the Center for International Blood and Marrow Transplant Research, we classified the conditioning regimens as myeloablative if total body irradiation >8 Gy, oral busulfan ≥9 mg/kg, i.v. busulfan ≥7.2 mg/kg, or melphalan >140 mg/m^2 was used in the conditioning regimen; otherwise, the conditioning regimen was classified as reduced intensity [18]. For patients with insufficient data regarding dosages of the agents used in the conditioning regimen, we used the information on conditioning intensity (myeloablative or reduced intensity) reported by the treating clinicians. We defined AML and ALL in first or second remission, CML in first or second chronic phase or accelerated phase, and MDS with refractory anemia or refractory anemia with ringed sideroblasts as standard risk, and all other conditions as high risk.

The following possible confounding variables were considered: recipient age group (0-5 years, 6-15 years, 16-49 years, or ≥50 years at transplantation), matching of ABO blood type between the recipient and UCB (match or major, minor, or bidirectional MM), recipient sex, sex MM between recipient and UCB (match, male donor–female recipient, or female donor–male recipient), disease (AML, ALL, CML, or MDS), disease status before transplantation (standard or high risk), type of conditioning regimen (myeloablative or reduced intensity), type of GVHD prophylaxis (calcineurin inhibitor plus methotrexate, calcineurin inhibitor only, others), and year of transplantation (1998-2004 or 2005-2009). Factors other than HLA MM and total nucleated cell (TNC) dose category were selected in a stepwise manner from the model with a variable retention criterion of $P < .05$. HLA MM and TNC dose category (≥10.0, 5.0-9.9, 2.5-4.9, 2.0-2.4, and $<2.0 \times 10^7$/kg) were then added to the final model. All tests were 2-sided, and a P value <.05 was considered statistically significant. All statistical analyses were performed with Stata version 12 (StataCorp, College Station, TX) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria) [19]. More precisely, EZR is a modified version of R commander (version 1.6-3) designed to add statistical functions used frequently used in biostatistics.

RESULTS

Patient Characteristics

Table 1 summarizes patient and transplant characteristics. The median age of the recipients at transplantation was 41 years (range, 0-82 years), and 2300 patients (77%) were age ≥16 years. Diagnoses for transplantation were AML in 1606 patients, ALL in 893, CML in 135, and MDS in 343. Half of the patients had standard-risk disease. UCBT was performed between 1998 and 2004 in 1153 patients (39%) and between 2005 and 2009 in 1824 patients (61%). The combination of a calcineurin inhibitor (tacrolimus or cyclosporine) and methotrexate was used in 62% of patients, whereas a calcineurin inhibitor alone was used in 22% of patients.

Some 40% of patients received a UCB unit containing $<2.5 \times 10^7$/kg TNCs, and 45% received a UCB unit containing 2.5-4.9 $\times 10^7$/kg TNCs. Roughly 12% of patients received $\geq 5.0 \times 10^7$/kg TNCs, but 93% of these patients were age <16 years. Median body weight was 17 kg (range, 4-68 kg) for the children and 55 kg (range, 24-165 kg) for the adults. HLA MM was categorized as follows: HLA match in both the GVH and HVG directions (GVH 0/HVG 0 MM group; n = 273 [9%]), 1-2 antigen MMs in the GVH direction but 0 MMs in the HVG direction (GVH 1-2/HVG 0 MM group; n = 150 [5%]), 1-2 antigen MMs in the HVG direction but 0 MM in the GVH direction (GVH 0/HVG 1-2 MM group; n = 136 [5%]), 1 antigen MM in both the GVH and HVG directions at the same locus (GVH 1/HVG 1 MM group; n = 716 [24%]), 2 antigen MMs in both the GVH and HVG directions (GVH 2/HVG 2 MM group; n = 1170 [39%]), 2 antigen MMs in the GVH direction and 1 antigen MM in the HVG direction (GVH 2/HVG 1 MM group; n = 231 [8%]), 1 antigen MM in the GVH direction and