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Comparison of Outcomes of 8/8 and 7/8 Allele–Matched Unrelated Bone Marrow Transplantation and Single-Unit Cord Blood Transplantation in Adults with Acute Leukemia

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A B S T R A C T

To investigate an up-to-date alternative donor selection strategy, we compared the transplantation outcomes of 8/8 and 7/8 allele–matched unrelated bone marrow transplantation (UBMT) with those of umbilical cord blood transplantation (UCBT) and redefined the role of UCBT with extended analysis. Using Cox and competing risk regression analyses, we analyzed the transplantation outcomes in adult patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). A total of 2472 first myeloablative transplantations between 2000 and 2010 were included (8/8 UBMT, 1001; 7/8 UBMT, 656; UCBT, 815). For acute and chronic graft-versus-host disease (GVHD) and nonrelapse mortality (NRM), we applied the combined analyses including both AML and ALL data. In the multivariate analyses, severe acute GVHD and NRM after UCBT were comparable with 8/8 UBMT, whereas those after 7/8 UBMT were significantly higher. The incidence of extensive chronic GVHD was significantly lower with UCBT compared with after 8/8 and 7/8 UBMT. With adjusted analyses for AML, UCBT and 8/8 UBMT showed similar overall survival (OS), whereas 7/8 UBMT showed inferior OS. For ALL, we found no significant difference in OS among the 3 groups. Cord blood may be the first choice alternative to 8/8 UBMT for both AML and ALL.

INTRODUCTION

Since human leukocyte antigen (HLA)-mismatched umbilical cord blood (UCB) transplantation (UCBT) was introduced as a treatment option for adult hematological disease around the year 2000 [1,2], transplantation outcomes with UCBT have gradually improved, and UCB has been assessed as an alternative donor source compared with unrelated bone marrow (BM) and peripheral blood stem cells [3-5]. Alternative donor selection criteria have been developed based on retrospective comparisons between unrelated donor transplantation (UDT) and UCBT [3-6]. Among HLA 8/8 allele–matched UDT, HLA 7/8 allele–matched UDT, and UCBT, HLA 8/8 allele–matched UDT has shown superior

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overall survival (OS) compared with 7/8 allele–matched UDT and UCBT, whereas a similar OS was shown for HLA 7/8 allele–matched UDT and UCBT [3,5,6]. Recipients of UCB have higher earlier mortality, including graft failure or severe infections, than recipients of UDT [3,4]. However, lower rates of chronic graft-versus-host disease (GVHD) and associated complications lead to lower long-term mortality, which compensates for the early deaths and results in survival similar to that with UDT [3,4,7]. Thus, the current consensus is that the first choice for an alternative donor is 8/8 UDT and that 7/8 UDT and UCBT are second-choice alternatives, which are expected to produce similar survival [6].

Both HLA matching and cell dose of the UCB unit have been demonstrated to be important factors influencing prognosis after UCBT [8]. Researchers from the Center for International Blood and Marrow Transplant Research and Eurocord have investigated the potential effect of HLA allele–level matching on outcomes of single-unit UCBT and revealed that neutrophil recovery is lower and nonrelapse mortality (NRM) is higher in allele-mismatched UCBT recipients than in the better matched UCBT [9,10]. However, patients in these studies consisted predominantly of children aged 16 years or younger (approximately 70%), and the median total nucleated cell count (TNCC) was 4.1×10^7/kg [8] and more than 5×10^7/kg recipient weight in most allele-mismatch groups [10], which may not be applicable to practice in adult UCBT. Because the median TNCC of single-unit UCBT in adult recipients is around 2.5×10^7/kg, a separate analysis is needed in adults to delineate the allele-mismatch effect of UCBT. In the Japanese population, we previously analyzed the HLA-mismatch effect in adult UCBT, but the analysis considered only serological typing for HLA-A and -B and allele typing for HLA-DRB1 [11]. Currently in Japan, a UCB unit is usually selected in terms of TNCC within serologically 2 loci mismatches out of 6 antigens between donor and recipient. In the present study, we also retrospectively analyzed the potential influence of allele mismatches on outcomes of UCBT.

We hypothesized that UCBT may demonstrate transplantation outcomes comparable to those of 8/8 allele–matched UDT in long-term analyses. Because most UDT in Japan still involves BM transplantation, the primary objective of the current study was to compare the transplantation outcomes of 8/8 and 7/8 allele–matched unrelated donor BM (UBM) transplantation (UBMT) with those of UCBT and to redefine the role of UCBT. Because UBMT and unrelated donor peripheral blood stem cell transplantation reportedly yield comparable survival outcomes, we believe that a comparison between UBMT and UCBT is relevant [12,13].

SUBJECTS AND METHODS

Data Collection and Source

The Japanese Society of Hematopoietic Cell Transplantation developed the Transplant Registry Unified Management Program (TRUMP), which is a unified database of 4 registries in Japan, including the Japan Marrow Donor Program, The Japan Cord Blood Bank Network, the Japanese Society of Pediatric Hematology/Oncology, and the Japan Society for Hematopoietic Cell Transplantation [14]. Physicians collect all data, primarily on-site, and send the data to Japanese Society of Hematopoietic Cell Transplantation through the TRUMP database. All transplantation data for the current study were obtained from the TRUMP database.

Patients

The inclusion criteria for the present study were as follows: (1) patients 16 to 50 years of age with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML), (2) first transplantation between January 2000 and December 2010, (3) myeloablative conditioning regimen, (4) UCB or UBM as the donor source, and (5) data for 6/6 HLA alleles or 8/8 HLA alleles available for UCBT and UBMT, respectively. The exclusion criteria were patients with (1) double-unit UCBT, (2) no GVHD prophylaxis, which probably indicated rescue UCBT after graft rejection, (3) in vivo T cell depletion (antithymocyte globulin, ATG), or (4) data missing regarding survival status or the date of last contact. After we applied the inclusion and exclusion criteria except for ATG use, the number of patients who underwent transplantation with ATG was 33. Thus, we considered that only a minor proportion of patients would be omitted from the analyses by excluding those who used ATG. The retrospective study protocol was approved by the institutional review board of the Japanese Red Cross Nagoya First Hospital, and written informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

HLA Typing and Donor Selection Strategy

Donor and recipient HLA typing data were obtained from the TRUMP database. Briefly, high-resolution typing was performed using the Luminex microbead method adjusted for the Japanese population and confirmed with the sequence-based typing for HLA-A, -B, -C, and -DRB1, as described elsewhere [15]. Low-resolution (serological or antigen level) disparities involved conversion of the DNA-based typing to its lower-level serologic equivalent, usually by translating the 4-digit typing data back to its first 2 digits.

For UBMT, all donor coordination is undertaken by the Japan Marrow Donor Program. High-resolution typing is applied for all donor and recipient pairs before transplantation, and a 7/8 allele–matched donor is selected if there were no potential 8/8 allele–matched donors. A common UCB unit selection strategy is to choose a UCB unit with the highest TNCC within 2-loci mismatch among HLA-A, -B, and -DR loci at the antigen level. The overall selection strategy for UBM donors and UCB units is almost identical with National Marrow Donor Program recommendations [6,16]. Donor choice between 7/8 allele–matched UBM donor and UCB is at the discretion of treating physicians and transplantation center practices.

Definitions

Neutrophil recovery was defined as an absolute neutrophil count of at least 500/μL for 3 consecutive time points. *Platelet recovery* was defined as a count of 50,000/μL without transfusion support. Diagnosis and clinical grading of acute and chronic GVHD were performed according to the established criteria [17,18]. *Relapse* was defined as a recurrence of the underlying hematological disease. *NRM* was defined as death during continuous remission. *Leukemia-free survival* (LFS) was defined as survival in a state of continuous remission.

Statistical Analysis

Because engraftment, acute and chronic GVHD, and NRM were not considered as the disease-specific outcomes, we applied the combined analyses including both AML and ALL data. For relapse, LFS and OS, we analyzed AML and ALL data separately. All categorical variables, such as patient, disease, and transplantation characteristics, were compared using chi-square statistics, and all quantitative variables such as age, weight, and cell dose were compared using the Kruskal-Wallis test (Table 1). The probabilities of OS and LFS were calculated using the Kaplan-Meier survival estimate [19]. The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, NRM, and relapse were calculated using the cumulative incidence estimate to consider competing risks [20]. For NRM, relapse was the competing risk, and for relapse, the competing risk was NRM. For hematopoietic recovery and acute and chronic GVHD, death without the event was the competing risk. For analysis of OS, death from any cause was considered an event. For analysis of LFS, relapse or death from any cause was considered an event. The log-rank test was used for group comparison.

Cox proportional hazards univariate and multivariate regression models were applied to identify significant risk factors for LFS and OS [21]. Competing risk regression models were applied for NRM, relapse, and acute and chronic GVHD. By utilizing the risk factors, a final multivariate regression model was constructed to assess the difference in graft sources at each endpoint. Multivariate models were built using a backward stepwise selection method with a threshold P value of less than .10. Results are expressed as relative risk (RR) with the 95% confidence interval (95% CI). Proportional hazards assumption was tested for all variables considered in multivariate analysis, and no violations occurred. Regardless of the level of significance, the main variable of interest, graft source (8/8 UBMT versus 7/8 UBMT versus UCBT), was considered in all steps of model construction. Other variables tested were patient age (16 to 40 versus >40 years), patient sex (male versus female), donor sex (male versus female), sex mismatch between donor and recipient (match versus male to female versus female to male), disease status at transplantation (standard risk versus advanced