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Clinical Research: Alternative Donors

A Comparison of Outcomes for Cord Blood Transplantation and Unrelated Bone Marrow Transplantation in Adult Aplastic Anemia

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A B S T R A C T

Earlier reports suggested that umbilical cord blood transplantation (UCBT) for aplastic anemia (AA) was feasible in alternative transplantation. To identify differences in outcomes of UCBT and HLA-matched or mismatched unrelated bone marrow transplantation (UBMT) in adults with AA, we analyzed registry data of the Japan Society for Hematopoietic Cell Transplantation and compared results of UCBT (n = 69) to 8/8-matched (n = 101), 7/8-matched (n = 65), or 6/8-matched (n = 37) UBMT. The transplantation period was from 2002 to 2012, and patients 16 years or older with AA were eligible. Median ages were 49, 35, 28, and 30 years for UCBT, 8/8-matched, 7/8-matched, and 6/8-matched UBMT, respectively. In multivariate analysis, risk of mortality was lower for 8/8-matched UBMT compared with that of UCBT (hazard ratio [HR], .55; 95% confidence interval [CI], .32 to .94; $P = .029$), adjusted for age and graft-versus-host disease (GVHD) prophylaxis, which were other associated factors. Mortality risks of 7/8-matched UBMT (HR, .55; 95% CI, .29 to 1.02) or 6/8-matched UBMT (HR, .67; 95% CI, .32 to 1.39) were not significantly different from those of UCBT. Risks of grade 3 or 4 acute and chronic GVHD were not different among the 4 groups. The most prevalent cause of death was graft failure in UCBT and 6/8-matched UBMT and infection in 8/8-matched and 7/8-matched UBMT. Under 40 years old,

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survival of UCBT was similar to that of UBMT (76%, 79%, 83%, and 83% for UCBT and 8/8-matched, 7/8-matched, and 6/8-matched UBMT, respectively, at 3 years), adjusted for transplantation period, which was another associated factor; however, for ages over 40 years, that of UCBT tended to be lower (47%, 64%, 64%, and 75% for UCBT, 8/8-matched, 7/8-matched, and 6/8-matched UBMT, respectively, at 3 years). To conclude, these data suggest that UCBT could be an alternative treatment option for younger adults when matched sibling or adequate UBMT donors are not available.

INTRODUCTION

Allogeneic stem cell transplantation from an HLA-matched sibling is the treatment of choice for children and young adult with aplastic anemia (AA) [1]. Transplantation outcomes for aplastic anemia from adult unrelated donors have improved over time and this expanded the transplantation indication to adults without a matched sibling donor [2-4]. Unrelated bone marrow transplantation (UBMT) matched at allele level for HLA-A, -B, -C, and -DRB1 (8/8-matched UBMT) for this disease is currently a widely accepted alternative donor transplantation of choice. However, 8/8-matched UBMT is not always available. In such cases, the next preferable alternative donor of choice is still not known.

Umbilical cord blood transplantation (UCBT) is a promising therapy for patients with malignant and nonmalignant hematological diseases [5]. Not all patients who lack a sibling donor can find a suitable alternative unrelated adult donor; for these patients, use of umbilical cord blood stem cells has extensively broadened the availability of stem cell transplantation for malignant diseases [6].

Earlier reports suggested the feasibility of UCBT for AA as an alternative transplant source. A report from the Japan Cord Blood Bank Network for both children and adults with AA showed 2-year overall survival of 41% [7]. Other previous reports have also shown the preferable results of UCBT for AA patients, including the pediatric population [8-10]. However, umbilical cord blood for adults with AA has not become the generally recommended alternative donor when an 8/8-matched UBMT donor is not available. UCBT results of the non–young adult population are further limited. As for whether or not UCBT can be chosen for adults with AA when a matched sibling or 8/8-matched UBMT donor are not available, we analyzed the outcome from registry data and compared the results of UCBT to 8/8-matched, 7/8-matched, and 6/8-matched UBMT.

METHODS

Data Collection

Data were obtained from the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the Japan Cord Blood Bank Network, and the Japan Marrow Donor Program [11-14]. Patient consent is not required, as the registry data of JSHCT consists of anonymized clinical information. The institutional review board of Nagoya University Graduate School of Medicine and the data management committees of the JSHCT approved this study, which was performed by the Donor Source, Adult Aplastic Anemia, and HLA Working Group of the JSHCT.

Inclusion Criteria

Patients included were 16 years and older with AA and received either UCBT or UBMT between 2002 and 2012. Excluded were patients who had prior allogeneic transplantation, myeloablative conditioning [15], infusion of 2 cord blood units, or infusion of bone marrow that were more than 2 of 8 HLA-mismatched at allele-level. Patients who were missing data concerning conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, or date of diagnosis were also excluded. Unrelated bone marrow donors were matched to patients at the allele level at HLA-A, -B, -C, and DRB1. However, matching of HLA-C was retrospectively performed at the time of analysis, as HLA-C had not been routinely typed for all cases at the time of transplantation until 2009. Two hundred ninety-six patients were eligible.

Endpoints

The primary endpoint of the study was overall survival (OS). Secondary endpoints were acute and chronic GVHD and neutrophil engraftment. *Overall mortality* was defined as death from any cause. Acute and chronic GVHD were evaluated as time to occurrence of GVHD, using standard criteria [16,17]. *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. Death without event was the competing risk for acute and chronic GVHD and neutrophil engraftment.

Statistical Analysis

Baseline patient and transplantation characteristics were compared using the chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. 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 neutrophil engraftment and acute and chronic GVHD were estimated based on a cumulative incidence method to accommodate competing risks.

To compare OS, Cox proportional hazard models were used to adjust for potential imbalance in baseline characteristics between the 4 treatment groups [18,19]; Fine and Gray proportional hazards models were used to compare acute and chronic GVHD and neutrophil engraftment. Multivariate models were built using a backward selection method with a threshold *P* value of less than .05. The main effect term, UCBT, and 3 HLA-mismatch levels for UBMT (ie, cord blood versus 8/8-matched versus 7/8-matched versus 6/8-matched bone marrow) were held in all steps of model building, regardless of the level of significance. Other variables considered were age at transplantation (≤39 versus ≥40 years), sex, recipient cytomegalovirus serostatus, interval from diagnosis to transplantation (<24 months versus ≥24 months), donor-recipient sex-mismatch status, transplantation preparative regimen (cyclophosphamide <100 mg/kg containing reduced-intensity conditioning [RIC] regimen versus cyclophosphamide ≥ 100 mg/kg containing RIC versus non-cyclophosphamide RIC), GVHD prophylaxis (cyclosporine-containing versus tacrolimus-containing), and period (2002 to 2007 versus 2008 to 2012). All variables met the proportionality assumption for Cox model. The effects of grades 2 to 4 and 3 or 4 acute and chronic GVHD were also tested for their effect on overall mortality as time-dependent covariates. Interactions between the main effect term and other covariates in the final model were tested and there were none. Results are expressed as hazard ratio (HR) together with the 95% confidence intervals. Stata version 13.1 (StataCorp, TX) was used in the analyses.

RESULTS

Characteristics of Patients

Table 1 shows characteristics of patients, their diseases, and transplantation regimens by the 4 treatment groups: cord blood, 8/8-matched, 7/8-matched, and 6/8-matched bone marrow. The median age of the UCBT recipients was 49 years whereas that of UBMT recipients was 35 years for 8/8-matched, 28 years for 7/8-matched, and 30 years for 6/8-matched UBMT recipients. The interval from diagnosis to transplantation was shorter for UCBT, and 70% of UCBT were performed within 24 months from the time of diagnosis. More bone marrow grafts were sex matched than cord blood. About 65% of UCBT recipients received a noncyclophosphamide RIC regimen. The majority (n = 42) of these 45 patients received a fludarabine/melphalan/total-body irradiation (TBI) regimen. Thirty-three of these patients received fludarabine 125 mg/m^2, melphalan 80 mg/m^2, and 4 Gy of TBI; the other 9 received modified doses of fludarabine, melphalan, and/or 2 Gy of TBI. Cyclophosphamide ≥ 100 mg/kg RIC preceded about 60% of UBMT. Only 3 UCBT recipients (4%) received in vivo T cell