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Favorable Outcome of Unrelated Cord Blood Transplantation for Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

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Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph^+ALL) is one of the highest-risk ALL groups. Whenever possible, patients with Ph^+ALL should undergo allogeneic hematopoietic stem cell transplantation (HSCT) after induction of remission. Although unrelated cord blood transplantation (CBT) has become a common treatment in adult patients who lack a sibling donor, data on the efficacy of CBT for Ph^+ALL are limited. We analyzed the clinical outcomes of 20 Ph^+ALL patients who underwent CBT (n = 8) or unrelated bone marrow transplantation (BMT) (n = 12). The median age was 41 years (range, 17-55 years). All but one of the patients were treated with an imatinib-based regimen before HSCT, and 19 patients were in first complete remission (CR) and 1 patient was in second CR at the time of HSCT. Seventeen patients received a myeloablative conditioning regimen containing 12 Gy of total-body irradiation, and 3 received a reduced-intensity conditioning regimen. After a median of 26 months of follow-up, estimated 3-year overall and leukemia-free survival rates were 100% and 85%, respectively, after CBT, and 49% and 38%, respectively, after unrelated BMT. The CBT group had significantly better overall survival than the BMT group ($P = .02$). Although *BCR-ABL* transcript was detected in 4 of 8 CBT patients at transplantation, 7 patients remained in molecular CR. Our findings suggest that CBT may be a viable option as post-induction therapy for Ph^+ALL in patients lacking a sibling donor.

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KEY WORDS: Ph^+ALL, CBT, Unrelated bone marrow transplantation, Imatinib, tyrosine kinase inhibitor

INTRODUCTION

Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph^+ALL) accounts for 20%-30% of cases of adult ALL [1]. Ph^+ALL is an aggressive disease with a poor prognosis, and it is not curable when treated by standard chemotherapy alone [2-5]. The results of recent clinical trials suggest that allogeneic hematopoietic stem cell transplantation (allo-HSCT) after imatinib-incorporating induction chemotherapy may be a promising option to overcome Ph^+ALL [6-10]. It is well accepted that allo-HSCT from an HLA-identical sibling donor offers the best outcome. Approximately 70% of patients lack a suitable sibling donor, however. In these patients, bone marrow (BM) from HLA-matched unrelated volunteer donors is usually selected as an alternative stem cell source [11]. In patients who lack a matched unrelated donor or require immediate transplantation due to the aggressive nature of the disease, unrelated cord blood (CB) may be a feasible alternative stem cell source. Recent comparative studies have shown similar outcomes of unrelated CB transplantation (CBT) and unrelated BM transplantation (BMT) in adult patients with acute leukemia [12-17]; however, there have been a few reports detailing the efficacy and safety of CBT in adult Ph^+ALL patients. In the present study, we compared the outcomes of unrelated CBT and unrelated BMT in adults with Ph^+ALL in complete remission (CR).

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PATIENTS AND METHODS

Patients

We analyzed clinical data from 20 consecutive adult (age 16 years or older) patients with Ph^+ALL in CR undergoing unrelated CBT (n = 8) or unrelated BMT (n = 12) at Tohoku University Hospital and Miyagi Cancer Center between June 2001 and April 2010. Patients lacking HLA-identical siblings were eligible for unrelated BMT from the Japan Marrow Donor Program as the first option. Patients were typed at the allele level at HLA-A, -B, and -DRB1, and received 6/6 or 5/6 allele-matched BM from unrelated donors. CBT was performed only in patients lacking a fully matched or one allele–mismatched unrelated donor or in those in which urgent transplantation was required due to disease status. Single-unit CB serologically matching at least 4 of 6 HLA antigens and containing $>2.0 \times 10^7$ nucleated cells/kg of body weight before freezing was obtained from the Japan Cord Blood Bank Network. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Treatment

The transplantation protocols were approved by the Institutional Review Boards of Tohoku University Hospital and Miyagi Cancer Center. Pretransplantation conditioning regimens included fractionated 12 Gy of total-body irradiation (TBI) and 120 mg/kg cyclophosphamide (CY) (n = 12); 12 Gy TBI, 8 g/m^2 cytosine arabinoside, and 120 mg/kg CY (n = 5); 125 mg/m^2 fludarabine (Flu) and 160-180 mg/m^2 melphalan (n = 2); and 150 mg/m^2 Flu, 120 mg/kg CY, and 4 Gy TBI (n = 1). Eighteen patients received tacrolimus and methotrexate (MTX), and the other 2 patients received cyclosporine and MTX as prophylaxis against graft-versus-host disease (GVHD). Tacrolimus or cyclosporine was administered i.v. starting on day -1. MTX was given i.v. at 10 mg/m^2 on day 1 and at 7 mg/m^2 on days 3 and 6. All patients received granulocyte colony-stimulating factor after transplantation until granulocyte recovery was achieved. Prophylaxis against infectious disease consisted of levofloxacin, fluconazole, acyclovir, and trimethoprim/sulfamethoxazole. Cyomegalovirus (CMV) monitoring was performed by CMV antigenemia once a week, and patients positive for CMV antigenemia were treated preemptively with ganciclovir.

Definitions

The time of neutrophil recovery was defined as the first of 3 consecutive days with an absolute neutrophil count of at least 0.5×10^9/L, and platelet recovery was defined by a platelet count of at least 20×10^9/L without transfusion support for 7 continuous days. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were graded according to established criteria [18,19]. Hematologic relapse was defined as the reappearance of any blasts in blood, >5% leukemic cells in BM, or extramedullary leukemia. Molecular relapse was defined as reversion to a positive polymerase chain reaction (PCR) assay for *BCR-ABL* transcripts. Treatment-related mortality (TRM) was defined as death without evidence of hematologic relapse.

Statistics

Patient characteristics were compared by the Mann-Whitney *U* test for continuous variables. Overall survival (OS) was measured from the date of transplantation until death or last follow-up. Leukemia-free survival (LFS) was measured from the date of transplantation until hematologic relapse, death from any cause, or last follow-up. Survival curves for OS and LFS were estimated by the Kaplan-Meier method and compared by the log-rank test. All *P* values were two-sided.

RESULTS

Characteristics of Patients and Donors

Characteristics of the patients, their donors, and their transplantation procedures are summarized in Table 1. The median age was 39 years (range, 17-55 years) in CBT recipients and 42 years (range, 24-55 years) in BMT recipients. The median white blood cell count at diagnosis was $7.7 \times 10^3/\mu L$ (range, $2.4\text{-}48 \times 10^3/\mu L$) in the CBT group and $48.6 \times 10^3/\mu L$ (range, $1.4\text{-}195 \times 10^3/\mu L$) in the BMT group ($P = .11$). Karyotype analysis revealed additional chromosomal abnormalities in 5 of 8 patients in the CBT group and in 5 of 12 patients in the BMT group. All patients but one were treated with imatinib in combination with standard chemotherapy before transplantation. Nineteen patients received HSCT while in first CR (CR1), and 1 patient received HSCT while in second CR (CR2). The median time from diagnosis to transplantation was 204 days (range, 169-303 days) in the CBT group and 216 days (range, 144-571 days) in the BMT group ($P = .46$).

Engraftment and GVHD

Neutrophil and platelet recovery were observed in all 20 patients. Median time to neutrophil engraftment was 21 days (range, 15-26 days) in patients undergoing CBT and 16 days (range, 12-18 days) in those undergoing BMT. The overall incidences of grade II-IV aGVHD and grade III-IV aGVHD up to day 100 posttransplantation were 50% and 0%, respectively, in the CBT group and 25% and 16.6%, respectively,