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Umbilical Cord Blood Transplantation after Reduced-Intensity Conditioning for Elderly Patients with Hematologic Diseases

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ABSTRACT

Although allogeneic hematopoietic stem cell transplantation is a potentially curative approach for advanced hematologic diseases, its application to elderly people is limited because of their comorbid physical conditions and lower chance of finding suitable related donors. Umbilical cord blood transplantation with reduced-intensity pretransplant conditioning (RI-UCBT) is 1 way to avoid these obstacles. We analyzed elderly patients aged 55 years and older with hematologic diseases who underwent RI-UCBT at our institute to assess feasibility and effectiveness of this treatment approach. Among the 70 patients included, 50 died, 74% of them from nonrelapse causes. Infection was the primary cause of death. Estimated overall survival and progression-free survival at 2 years were both 23%. In multivariate analyses, standard-risk diseases, age younger than 61 years, grade 0-II acute graft-versus-host disease, and the absence of preengraftment immune reaction were significantly associated with better overall survival. RI-UCBT is a potentially curative and applicable approach for elderly patients. Higher mortality, especially from nonrelapse causes, is the biggest problem to be solved to increase the feasibility of this approach.

KEY WORDS

Cord blood transplantation • Reduced intensity • Elderly patients • Hematologic diseases

INTRODUCTION

Although morbidity associated with hematologic malignant diseases in elderly patients is higher than that in younger patients [1], elderly patients are less likely to be candidates for allogeneic stem cell transplantation, because of the fact that they are more likely to have comorbid organ conditions, either clinically or subclinically, which result in a higher rate of procedure-related mortality [2], and that they are less likely to have HLA-matched related donors available, as siblings also tend to be elderly.

The development of reduced-intensity conditioning (RIC) for transplants, which results in less toxicity and depends largely on graft-versus-tumor effects rather than high-dose therapy to eliminate malignant cells, has been shown to allow elderly patients to undergo allogeneic transplants [3-5]. The use of umbilical cord blood transplantation (UCBT) has been increasing because of the potential advantage of rapid availability and the lower risk of graft-versus-host disease (GVHD), thus permitting less stringent HLA matching [6,7]. The outcome of UCBT has been reported to be similar to unrelated bone marrow in the myeloablative setting [8-10]. UCBT with reduced-intensity pretransplant conditioning (RI-UCBT) for adults, mostly younger than 55 years old, has been increasingly reported, and has been shown to be applicable even in patients with a relatively low number of nucleated cells for their body weight [11-16]. However, little information has been available on whether elderly patients can tolerate slower engraftment, more infectious complications [17], and the unique preengraftment immune reaction (PIR) associated with UCBT [18,19]. PIR has been described by us and others [18,19], characterized

by the symptoms induced possibly by hypercytokinemia, which sometimes cause severe organ damage and fatal outcome. We therefore retrospectively evaluated the use of the RI-UCBT in patients aged 55 and older by analyzing engraftment, nonrelapse mortality (NRM), GVHD, progression-free (PFS), and overall survival (OS) to address the feasibility and effectiveness of this method in older patients.

PATIENTS, MATERIALS, AND METHODS

Patients

This study included patients aged 55 and older who underwent RI-UCBT at our institute from July 18, 2002 through October 28, 2005. Patients were eligible for this study if they had any hematologic malignancies at high risk for relapse or severe aplastic anemia (AA) refractory to standard immunosuppressive therapy, as well as if they were unable to find suitable related or unrelated bone marrow (BM)/peripheral blood (PB) donors within reasonable time periods relative to their disease conditions. Patients with acute leukemia could be at first remission but at high risk for relapse because of adverse cytogenetic abnormalities, have a prior hematologic disorder, or be at any status beyond first remission. Patients with myelodysplastic syndrome (MDS) had to be refractory anemia with excess of blasts or chronic myelomonocytic leukemia, or have refractory anemia with transfusion dependency and/or severe neutropenia. Patients with chronic myeloid leukemia (CML) had to be beyond the first chronic phase. Lymphoma patients had to be beyond the first remission except those with acute or lymphoma type adult T cell leukemia. Patients who had end-stage organ dysfunction (DLco <30% predicted or LVEF <35%), or active serious infection at the time of transplantation were not eligible. All patients gave written informed consent, and the study was approved by the appropriate institutional review boards.

Donor Selection

UCB units were obtained from Japanese Cord Blood Bank Network. HLA-A and HLA-B antigens were identified by serologic typing. HLA-DRB1 alleles were determined by high-resolution molecular typing using polymerase chain reaction (PCR) sequence-specific primers. UCB grafts had at least 4 of 6 HLA-A, B antigens, and DRB1 alleles that were matched to the recipient and had a cryopreserved cell dose of at least 1.8×10^7 nucleated cells per kg of recipient body weight. The median total nucleated cell number and median $CD34^+$ cell number were 2.8 (range: 1.8–5.2) $\times 10^7$/kg and 0.84 (0.11-3.28) $\times 10^5$/kg, respectively.

Patient Characteristics

Seventy consecutive patients were included in this study. Their characteristics are shown in Table 1.

Table 1. *Patient and Donor Umbilical Cord Blood Characteristics*

Characteristic	No. (%) of Patients
Sex	
Male	45 (64)
Female	25 (36)
Age (years)	
Median (range)	61 (55-79)
Age distribution (years)	
55 to 59	31 (44)
60 to 64	16 (23)
65 to 69	17 (24)
At least 70	6 (9)
Diagnosis	
AML	28 (40)
MDS	3 (4)
CML	4 (6)
ALL	11 (16)
NHL	8 (11)
ATL	12 (17)
MM	1 (1)
PCL	1 (1)
AA	2 (3)
HCT-CI	
0	24 (34)
1	25 (36)
2	11 (16)
3 or greater	10 (14)
History of prior chemotherapy	
Yes	59 (84)
No	11 (16)
History of prior documented infections	
Yes	15 (21)
No	55 (79)
Disease status	
Standard risk	15 (21)
High risk	55 (79)
Conditioning regimen	
Flu/Mel/TBI	65 (93)
Flu/Bu/TBI	4 (6)
Others	1 (1)
GVHD prophylaxis	
Cyclosporine A alone	37 (53)
Tacrolimus alone	33 (47)
HLA disparity to UCB	
5/6	9 (13)
4/6	61 (87)
Sex mismatch to UCB	
Yes	51 (73)
No	19 (27)

AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; ATL, adult T cell leukemia; MM, multiple myeloma; PCL, plasma cell leukemia; AA, aplastic anemia; Flu, fludarabine; Mel, melphalan; TBI, total body irradiation; Bu, busulfan; UCB, umbilical cord blood: HCT-CI, hematopoietic cell transplantation-specific comorbidity index.

Of these 70 patients, 25 were women and 45 were men. Their median age was 61 years (range: 55-79 years). The patients' diagnoses included acute myeloid leukemia (AML; n = 28), acute lymphoblastic leukemia (ALL; n = 11), MDS (n = 3), CML (n = 4), non-Hodgkin lymphoma (NHL; n = 8), adult T cell