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Comparable Long-Term Outcome of Unrelated Cord Blood Transplantation with Related Bone Marrow or Peripheral Blood Stem Cell Transplantation in Patients Aged 45 Years or Older with Hematologic Malignancies after Myeloablative Conditioning

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A B S T R A C T

We investigated whether bone marrow or peripheral blood stem cells from older sibling donors or cord blood from unrelated donors provided a better outcome in allogeneic hematopoietic stem cell transplantation for relatively older patients who were candidates for myeloablative conditioning. Clinical outcomes of 97 patients aged 45 years or older with hematologic malignancies who received unrelated cord blood transplantation (CBT) (n = 66) or bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) from related donors (n = 31) were compared. The cumulative incidences of grades III to IV acute and extensive chronic graft-versus-host diseases were similar between both groups. Although transplant-related mortality was significantly lower after CBT compared with BMT/PBSCT from related donors (hazard ratio [HR], .29, $P = .04$), overall mortality (HR, .72, $P = .47$) and relapse (HR, 2.02, $P = .23$) were not significantly different after CBT and BMT/PBSCT from related donors. These data suggest that CBT could be as safe and effective as BMT/PBSCT from older related donors for relatively older patients when it is used as a primary unrelated stem cell source.

INTRODUCTION

Donor age has been associated with transplant outcomes in allogeneic hematopoietic stem cell transplantation (allo-HSCT) after myeloablative conditioning or reduced-intensity conditioning (RIC) [1-5]. Older donor age resulted in an increased incidence of severe graft-versus-host disease (GVHD), which led to higher transplant-related mortality (TRM) or overall mortality after allo-HSCT from unrelated adult donors [1,2]. In contrast, it is difficult to determine the exact effect of the age of related donors, because increasing recipient age is frequently accompanied by increased donor age after allo-HSCT from related donors. However, older donor age of related donors may also be associated with adverse outcomes [3-5].

Several studies, including ours, comparing both cord blood transplantation (CBT) and bone marrow transplantation (BMT)/peripheral blood stem cell transplantation (PBSCT) from unrelated donors after myeloablative conditioning in adult patients demonstrated that the incidence of severe GVHD was significantly lower after CBT than after unrelated BMT/PBSCT. The survival rate and relapse incidence in CBT recipients were comparable with those in unrelated BMT/PBSCT recipients [6-9]. Moreover, we also demonstrated similar survival, relapse, and TRM between unrelated CBT and related BMT/PBSCT (rBMT/PBSCT) recipients [10]. The incidences of grades III to IV acute GVHD (aGVHD) and extensive chronic GVHD (cGVHD) among CBT recipients were also significantly lower than those among rBMT/PBSCT recipients. Because the lower risk of severe GVHD is one of the most attractive advantages of CBT, the use of cord blood instead of bone marrow or mobilized peripheral blood as a stem cell source might offer the possibility of decreasing severe GVHD in older patients. However, there has been no comparative study between CBT and BMT/PBSCT from older related donors after myeloablative conditioning in relatively older patients.

We previously reported that unrelated CBT after myeloablative conditioning is feasible in patients over the age of 45 years [11,12]. In this retrospective study, we report on a clinical comparison of CBT from unrelated donors and BMT/PBSCT from older related donors in patients older than 45 years of age with hematologic malignancies who were candidates for a myeloablative conditioning.

METHODS

Patients and Transplant Procedures

This retrospective study included 97 consecutive patients, 45 years of age or older, who received CBT (n = 66) from unrelated donors or BMT (n = 26) or PBSCT (n = 5) from related donors for acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and non-Hodgkin lymphoma (NHL) at the Institute of Medical Science, University of Tokyo between May 1992 and July 2013. Nineteen patients who received rBMT/PBSCT and 32 patients who received CBT were included from our previous study with extended

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Table 1
Characteristics of Patients, Grafts, and Transplantation

Characteristic	rBMT/PBSCT	CBT	*P*
Number of patients	31	66	
Recipient age, yr, median (range)	48 (45-58)	49 (45-55)	.60
Recipient sex, n (%)			.51
Male	20 (64)	37 (56)	
Female	11 (35)	29 (43)	
Recipient CMV serostatus, n (%)			.18
Positive	28 (90)	64 (96)	
Negative	0 (0)	2 (3)	
Unknown	3 (9)	0 (0)	
Disease type, n (%)			.08
AML	16 (51)	44 (66)	
MDS	2 (6)	8 (12)	
CML	6 (19)	3 (4)	
ALL	3 (9)	8 (12)	
NHL	4 (12)	3 (4)	
Disease status at transplantation,* n (%)			.48
Standard	8 (25)	23 (34)	
High	23 (74)	43 (65)	
Conditioning regimen, n (%)			<.01
TBI12Gy+Ara-C/G-CSF	21 (64)	0 (0)	
TBI12Gy+Ara-C/G-CSF+CY	2 (6)	52 (78)	
TBI12Gy+Ara-C/G-CSF+Flu	0 (0)	3 (4)	
TBI12Gy+CY	3 (9)	3 (4)	
TBI12Gy+Ara-C+CY	1 (3)	8 (12)	
TBI12Gy+VP16	4 (12)	0 (0)	
GVHD prophylaxis, n (%)			.23
Cyclosporine A+methotrexate	29 (93)	65 (98)	
Cyclosporine A	2 (6)	1 (1)	
Number of nucleated cells, $\times 10^7$/kg, median (range)	26.6 (3.13-50.0)‡	2.39 (1.72-5.07)	<.01
Number of CD34$^+$ cells, $\times 10^5$/kg, median (range)	40.5 (20.6-75.0)§	1.04 (.17-3.15)	<.01
Donor age, yr, median (range)	46.5 (38-58)	—	—
Sex compatibility, n (%)			.81
Female donor to male recipient	8 (25)	20 (30)	
Other	23 (74)	46 (69)	
HLA disparities,† n (%)			<.01
0	28 (90)	1 (1)	
1	2 (6)	13 (19)	
2	1 (3)	52 (78)	
ABO incompatibility, n (%)			.04
Match	19 (61)	20 (30)	
Major mismatch	4 (12)	17 (25)	
Minor mismatch	5 (16)	18 (27)	
Bidirectional mismatch	3 (9)	11 (16)	
Time from diagnosis to transplantation, days, median (range)	521 (59-2501)	390.5 (55-6783)	.84
<365 d, n (%)	12 (38)	31 (46)	.51
≥365 d, n (%)	19 (61)	35 (53)	
Year of transplantation, n (%)			<.01
1992-2002	27 (87)	17 (25)	
2003-2013	4 (12)	49 (74)	
Follow-up for survivors, mo, median (range)	185 (32-258)	87 (4-175)	<.01

CMV indicates cytomegalovirus; CY, cyclophosphamide; Flu, fludarabine; VP-16, etoposide.

* Disease status at transplantation was classified as standard risk or high risk; CR1 or CR2 without poor prognostic karyotype for AML and ALL, refractory anemia for MDS, chronic phase for CML, and CR1 or CR2 for NHL were classified as standard risk, whereas patients in all other situations were classified as high risk.

† Number of HLA disparities defined as low resolution for HLA-A, -B, and -DR.

‡ Number of nucleated cells was only for BMT recipients.

§ Number of CD34$^+$ cells was only for PBSCT recipients.

follow-up [10]. For disease status at transplantation, patients in first complete remission (CR1) or second complete remission (CR2) without poor prognostic karyotype for AML and ALL, refractory anemia for MDS, chronic phase for CML, and CR1 or CR2 for NHL were classified as standard risk, whereas patients in all other situations were classified as high risk.

Although bone marrow or mobilized peripheral blood from HLA-compatible related donors within immediate families is a frontline graft source, patients without a suitable closely HLA-compatible related donor were eligible for CBT as an alternative first treatment option, unless they had any type of anti-HLA antibody. Cord blood units were obtained from the Japan Cord Blood Bank Network and were selected as reported previously [9,10]. All patients received 12 Gy total body irradiation (TBI)-based myeloablative conditioning regimens, and cyclosporine-based GVHD prophylaxis regimens, as previously reported [9,10]. For myeloid disease, granulocyte colony-stimulating factor (G-CSF) was added to the conditioning regimen to increase the susceptibility to cytosine arabinoside (Ara-C) through induction of cell cycle entry of dormant leukemia cells, as previously reported [10]. Almost all patients received some supportive care, such as antibacterial, antifungal and antiviral agents, as previously reported [9,10]. The institutional review board of the Institute of Medical Science, University of Tokyo approved this study, which was conducted in accordance with the Declaration of Helsinki.

End Points and Definitions

The primary study end point was overall survival (OS), which was defined as the time from the date of transplantation to the date of death or last contact. Secondary end points were relapse, TRM, GVHD, and neutrophil and platelet recovery. Relapse was defined by morphologic evidence of disease in peripheral blood, bone marrow, or extramedullary sites. TRM was defined as death during a remission. Both aGVHD and cGVHD were graded according to previously published criteria [13,14]. The incidence of aGVHD