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Which donor is better when a matched donor is not available domestically? Comparison of outcomes of allogeneic stem cell transplantation with haploidentical and international donors in a homogenous ethnic population

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ABSTRACT

A substantial proportion of patients requiring allogeneic stem cell transplantation (alloSCT) do not have a human leukocyte antigen-matched sibling donor and need an alternative donor. In this multicenter retrospective study, we compared the outcomes of 176 patients with myelodysplastic syndrome and acute leukemia undergoing alloSCT from haploidentical (n = 121) and international (n = 55) donors between 2002 and 2016. For recipients of haploidentical and international donors, the 2-year overall survival rates were 33.4% and 35.3%, respectively (P = 0.347), and relapse-free survival rates were 31.7% and 34.4% (P = 0.264), respectively. In addition, there were no significant differences in the cumulative incidences of acute and chronic graft versus host disease or incidences of infection within 30 days (all $P > 0.05$). Similarly, there were no significant differences in these measures for acute leukemia patients (n = 143; all $P > 0.05$). A multivariate analysis revealed that the donor type was not an independent prognostic or predictive factor. These data suggest that both haploidentical and international donors are feasible alternative sources for alloSCT when a matched donor is not available domestically.

1. Introduction

The survival rate for patients with hematologic malignancies has been greatly improved by the development of targeted therapy, immunotherapy, and transplantation [1–3]. Particularly, allogeneic stem cell transplantation (alloSCT) has been identified as a curative treatment modality in hematologic malignancies [2], improving the 3-year overall survival (OS) of leukemia patients to 60–70% [4,5].

Traditionally, human leukocyte antigen (HLA)-matched related donors (MRD) are selected for alloSCT due to the superior outcomes compared with those from unrelated or HLA-mismatched donors. However, with the use of T-cell-depleted modalities, including prophylactic antithymocyte globulin (ATG) and post-transplantation cyclophosphamide (postCy), survival outcomes with alloSCT from unrelated or haploidentical donors have improved dramatically, approximating the survival outcomes of alloSCT from MRD [6,7].

In practice, the probability of finding MRD is limited to only 25% for patients who have one sibling. With the decrease in birthrate in developed countries, donor sources other than MRD, particularly, unrelated matched donors, are increasingly being used for alloSCT. In South Korea, unrelated donor sources for alloSCT are identified by the Korean Marrow Donor Program (KMDP). In patients for whom there are no appropriate MRD or unrelated donors from the KMDP, haploidentical or international donors are used for alloSCT. However, it is not known which donor is better for alloSCT in this homogeneous ethnic country.

Here, we performed a multicenter retrospective study at four hospitals in South Korea to compare the survival outcomes and

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Table 1
Baseline characteristics of patients.

Characteristic	Total (n = 176)	Donor type		P value
		Haploidentical (n = 121)	International (n = 55)	
Age, years (median [range])	41 (16–67)	46 (16–66)	36 (18–67)	0.026
Sex, no. (%)				
Male	115 (65.3)	76 (62.8)	39 (70.9)	0.295
Female	61 (34.7)	45 (37.2)	16 (29.1)	
Period, no. (%)				
Early (12/2002–10/2009)	48 (27.3)	11 (9.1)	37 (67.3)	< 0.001
Late (11/2009–04/2016)	128 (72.7)	110 (90.9)	18 (32.7)	
Source, no. (%)				
Bone marrow	18 (10.2)	2 (1.7)	16 (29.1)	< 0.001
Peripheral blood	158 (89.8)	119 (98.3)	39 (70.9)	
Disease, no. (%)				
Acute leukemia	143 (81.3)	98 (81.0)	45 (81.8)	0.896
MDS	33 (18.8)	23 (19.0)	10 (18.2)	
Conditioning regimen, no. (%)				
Myeloablative	36 (20.5)	15 (12.4)	21 (38.2)	< 0.001
Bu-Cy based	22 (12.5)	9 (7.4)	13 (23.6)	
TBI-Cy based	14 (8.0)	6 (5.0)	8 (14.5)	
Reduced intensity	140 (79.5)	106 (87.6)	34 (61.8)	
Bu-Flu-ATG based	125 (71.0)	101 (83.5)	24 (43.6)	
TBI-Flu based	4 (2.3)	0	4 (7.3)	
Flu-Cy	2 (1.1)	2 (1.7)	0	
*Others	9 (5.1)	3 (2.5)	6 (10.9)	
Disease status, no. (%)				
CR	104 (59.1)	70 (57.9)	34 (61.8)	0.879
Non-CR	37 (21.0)	26 (21.5)	11 (20.0)	
Not applicable	35 (19.9)	25 (20.7)	10 (18.2)	
Disease risk index				
High	56 (31.8)	40 (33.1)	16 (29.1)	0.377
Intermediate	99 (56.3)	77 (63.6)	22 (40.0)	
Low	0	0	0	
Unknown	21 (11.9)	4 (3.3)	17 (30.9)	
HLA, no. (%)				
Full matched	38 (21.6)	0	38 (69.1)	< 0.001
Mismatched	138 (78.4)	121 (100.0)	**17 (30.9)	
$CD34^+$ cells, 10^6/kg (median [range])	5.3 (0.9–23.3)	5.4 (0.9–12.1)	4.8 (1.0–23.3)	0.432

Abbreviations: MDS, myelodysplastic syndrome; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; Flu, fludarabine; ATG, antithymocyte globulin; CR, complete remission; HLA, human leukocyte antigen. *Other regimens included Bu-Flu-alemtuzumab and Flu-melphalan. **80–90% HLA-matched donor.

complications of patients with hematologic malignancies (myelodysplastic syndrome [MDS]/acute leukemia) undergoing alloSCT from haploidentical and international donors.

2. Materials and methods

2.1. Patient population

We retrospectively recruited patients diagnosed with MDS and acute leukemia who had undergone alloSCT from either haploidentical or international donors at Seoul National University Hospital, Samsung Medical Center, Kyungpook National University Hospital, and the National Cancer Center between December 2002 and April 2016. The alloSCTs performed during this time were divided into those occurring during an early period (December 2002 through October 2009) and a late period (November 2009 through April 2016). The international donors were from Japan, China, Germany, the United States of America, Australia, and Taiwan. The characteristics of the patients and information associated with alloSCT, such as conditioning chemotherapy, donor type, the dose of $CD34^+$ cells, disease status at the time of alloSCT, disease risk index, and whether transplants were from HLA-matched or unmatched donors, were collected by reviewing the medical records. The disease risk index was classified according to cytogenetics and the disease status [8].

2.2. Transplantation

All patients received conditioning chemotherapy, which was followed by alloSCT. The day of stem cell infusion was designated as day 0. The conditioning regimens consisted of myeloablative (MA) or reduced intensity conditioning (RIC) regimens. The MA conditioning regimens were either busulfan (Bu) and cyclophosphamide (Cy) or total body irradiation (TBI) and Cy. The RIC regimens consisted of Bu, fludarabine (Flu), and ATG, TBI-Flu, Flu-Cy, Bu-Flu-alemtuzumab, or Flu-melphalan. All patients received recombinant granulocyte colony-stimulating factor from day 1 of stem cell transplantation until the absolute neutrophil counts were > 1000/μL for three consecutive days. Patients were treated with cyclosporine or tacrolimus with or without a short course of methotrexate (days 1, 3, 6, and 10) as graft versus host disease (GVHD) prophylaxis.

2.3. Statistical analysis

Categorical variables were compared using Pearson's chi-square or Fisher's exact tests, as appropriate. Independent t tests were used for comparing continuous variables. Time to relapse (TTR), relapse-free survival (RFS), OS, and the cumulative incidence of chronic GVHD were estimated using Kaplan–Meier analyses. TTR, RFS, and OS were defined as the times from the alloSCT (day 0) to the date of disease relapse, disease relapse or death, and death or the last follow-up, respectively. The median values of continuous variables were used as the cutoff values. Clinical variables with P values of < 0.2 in the univariate analyses were included in the multivariate analyses performed using the Cox proportional hazard model. All statistical tests were two sided, and significance was defined as a P value of < 0.05. All analyses were performed with SPSS version 22.0 (IBM, Armonk, NY, USA).

2.4. Ethical considerations

This study was reviewed and approved by the institutional review board of each participating hospital. This study was conducted in accordance with the precepts established by the Declaration of Helsinki for biomedical research.

3. Results

3.1. Patient characteristics

Of the 176 patients included in the study, 121 underwent alloSCT from haploidentical-related donors and 55 had international donors from Taiwan (n = 14), the United States of America (n = 13), Japan (n = 11), China (n = 10), Germany (n = 1), and Australia (n = 1); countries of origin were not recorded from five donors. The baseline clinical characteristics of the patients receiving transplants from either international or haploidentical donors were compared and are summarized in Table 1. There were significant differences between the groups for the age of the patient at the time of alloSCT, the type of donor according to the study period (early or late period), the source of the transplant, the type of conditioning chemotherapy regimen, and the degree of HLA matching. The degrees of HLA matching in the haploidentical donor group were 6/10 (n = 4 patients), 5/10 (n = 1), 7/8 (n = 6), 6/8 (n = 8), 5/8 (n = 26), 4/8 (n = 47), 5/6 (n = 2), 4/6 (n = 5), and 3/6 HLA matching (n = 20); the degree of HLA matching