Hematopoietic Stem Cell Transplantation with Using Multinational Unrelated Donors for Acute Myelogenous Leukemia

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Background: Many AML patients have received hematopoietic stem cell transplantation (HSCT) from HLA-matched unrelated donors. According to many of the previous reports, those patients could achieve long-term, disease-free survival after HSCT from multinational unrelated donors with tolerable transplant-related complications, even when there are HLA-mismatches.

Methods: We present the results of 35 unrelated hematopoietic stem cell transplantations from multiple international donor banks including the Korean (n=24), and Japan Marrow Donor Program (n=3), the Taiwan Tzu Chi Marrow Donation Registry (n=6), as well as using Caucasian donors from the National Marrow Donor Program (n=2), for the treatment of AML patients.

Results: The median age of patients was 36 (range: 16～53) and the median follow-up duration was 21 months (range: 5～60). Also, the median age of the donors was 28 (range: 20～53). The majority of the patients had intermediate or unfavorable cytogenetic features. The main conditioning regimen we used consisted of cyclophosphamide plus TBI (n=31) with our standard GvHD prophylaxis that contained tacrolimus plus a short course of methotrexate. Some patients (n=10) received an additional two-day course of ATG (thymoglobulin, Sangstat) in addition to the standard regimen. All the transplanted patients achieved engraftment. The incidence of acute GvHD was 42%, and that of chronic GvHD was 56%. Four (11%) patients have relapsed to date. The two-year non-relapse transplant-related mortality was 26%. The estimated probability of DFS and the event-free survival at five-years were 80% and 53%, respectively.

Conclusion: These results suggest that multinational unrelated donors HSCT may provide a feasible option for the treatment of high-risk Korean AML patients. ***(Korean J Hematol 2007;42:98-105.)***

Key Words: Multinational unrelated donor, HSCT, AML, GvHD

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INTRODUCTION

With many international or loco-regional bone marrow donor search registries worldwide, unrelated donors may be found for patients who do not have an HLA-identical sibling.[1] Interestingly, as shown in the recent EBMT report, transplant rates were higher and increasing use of unrelated donors was more pronounced in absolute numbers in European countries with high income.[2] Many AML patients without an HLA matched sibling have received hematopoietic stem cell transplantation (HSCT) from HLA-matched unrelated donors. According to many reports so far, those patients with AML could result in long-term disease-free survival after unrelated donor HSCT.[3,4] However, although the clinical outcome after unrelated donor HSCT has much improved, obstacles still include the long donor search time and high transplant-related mortality (TRM).[5,6] Further, even for the majority of patients who lack HLA-matched unrelated donors, immunogenetic research is focused on the identification of tolerable HLA mismatches.[7] Most of all, perfect donor-recipient HLA matching is critical to the optimal results of unrelated HSCT.[8,9]

The first Korean unrelated donor search program at the Catholic Hematopoietic Stem Cell Information Bank was established in 1994 to facilitate donor search for stem cell donation in patients without an HLA matched sibling. Since several registries with HLA-typed volunteer donors have been established in Japan, Taiwan and Korea, more precise tissue typing technology can be utilized to clearly differentiate matched from mismatched unrelated donors. Therefore, with the use of different immunosuppression regimens and supportive care, according to the patient's risk factors, HLA-mismatched HSCT using multinational unrelated donors may be an additional option for patients.

Analysis of our data indicates that transplantation with multinational unrelated donors, with HLA-mismatches, can result in successful long-term disease-free survival together with event-free survival with tolerable TRCs. These findings suggest that the use of multinational donor banks may expand the pool of available donors for more standard-risk AML patients.

MATERIALS AND METHODS

1. Patients' characteristics

We present the results of HLA-mismatched HSCT using available unrelated Asian donors from the Japan Marrow Donor Program (JMDP), Taiwan Tzu Chi Marrow Donation Registry (TCMDR), as well as Caucasian donors from the National Marrow Donor Program (NMDP) beginning from 1998. Korean patients with intermediate- and high-risk AML who did not have suitable HLA-matched related or unrelated donors were enrolled. Generally, they are categorized as high-risk for acute graft-versus-host disease (GvHD) and other transplant-related complications (TRCs) post-transplant, based on the impact of HLA allele(s) or antigen mismatch immunobiology on clinical outcomes. Beginning in December 2001, 35 consecutive adult AML patients, with a variety of baseline clinical conditions, and a median age of 36 years (range: 16～53) underwent transplantation at the Catholic Hemopoietic Stem Cell Transplantation Center of Korea; follow-up was carried out through November 2006. The median follow-up duration was 21 months (range: 6～60). After the scheduled course of consolidation chemotherapy, for patients younger than 65 years of age complete remission (CR) was observed in 29 patients and incomplete remission (IR) or a refractory state was identified in six; these patients were assigned to receive an HLA-mismatched unrelated HSCT if an HLA-identical related or unrelated donor was not available. All patients, except for patients who received HSCT before year 2003 (n=15), who were scheduled to receive allogenic trans-

plantation from HLA-mismatched unrelated donors based on assessments at the level of the HLA-Cw antigen or 1～2 alleles at the HLA-A, -B, and -DR loci, were screened for HLA-A, -B, -Cw, and -DRB1 alleles using a high-resolution DNA sequencing molecular typing method. According to our protocol for unrelated donor searches we primarily started with the domestic donor registry, and then secondarily used other Asian donor registries (Japan and Taiwan). Thereafter, we finally used the America (NMDP) and European (Zentrales Knochenmarkspender-Register Deutschland, ZKRD) donor registries if we could not find appropriate unrelated donors throughout Asia. The median time to transplantation from CR was six months (range: 4～10). All patients were included in the long-term follow-up analysis post-transplant. The details of the clinical features of the patients and donors at the time of transplantation are summarized in Table 1.

Cytogenetic risk groups were classified using the guidelines reported by the SWOG trial.[10] Briefly, normal karyotypes in addition to +8, −Y, +6, and del(12p) chromosome abnormalities at presentation were considered to represent an intermediate risk group (n=18). However, if there was not the presence of t(15;17) or inv(16)/t(16;16)/del(16q) with any other abnormality, and t(8;21) without del(9q) or complex karyotypes at presentation, all other specific cytogenetic abnormalities were deemed unfavourable (n=17).

Table 1. Characteristics of donors (D) and AML recipients (R) in this study

Parameters	Number, n=35
Age, D/R; median years (range)	28 (20～53)/36 (16～53)
Sex, D/R; male : female	24 : 11/21 : 14
Sex matching	
M→M	14
M→F	10
F→M	7
F→F	4
ABO matching	
Match	13
Major mismatch	8
Minor mismatch	12
Major/minor mismatch	2
Diagnosis, FAB classification	
M0	4
M1	2
M2	15
M4	5
M5	1
M6	2
Secondary AML	5
Hypoplastic	1
Registries	
CHIB, Korea	4
KMDP, Korea	20
TCMDR, Taiwan	6
JMDP, Japan	3
NMDP, USA	2
Mismatch grade of HLA	
1 allele	14
2 alleles	4
1 antigen	11
1 antigen+1 allele	6
Stem cell sources	
Bone marrow	29
Peripheral blood	6
Pre-transplant status	
1st complete remission	25
2nd complete remission	4
Incomplete remission or refractory	6

2. Induction and consolidation chemotherapy

All patients were treated according to our centre's standard protocol, which consists of '3×7' idarubicin (IDA) plus N4-behenoyl-1-β-D-arabinofuranosyl cytosine (BH-AC) induction chemotherapy.[11] Briefly, IDA was administered daily at a dose of 12mg/m^2 for 30 min intravenously for three consecutive days, and BH-AC was administered daily at a dose of 300mg/m^2 over a period of 4 h for seven consecutive days, as previously reported.[11] For all AML patients enrolled in this study, we used the same AML induction and consolidation strategy. This consolidation chemotherapy was repeated for one to two courses based on the donor search results and the patients' clinical condition. The first consolidation chemotherapy consisted of either a combination

of BH-AC (300mg/m^2 intravenously for five days) and IDA (12mg/m^2 intravenously for three days) (n=35). For the second consolidation chemotherapy, a combination of mitoxantrone (12 mg/m^2 intravenously for three days) and etoposide (100mg/m^2 intravenously for five days) was administered (n=18).

3. Transplantations from mismatched unrelated donors

Overall, 29 patients received unrelated donor bone marrow (BM) cells whether they were in CR or not, and six patients received G-CSF mobilized peripheral blood stem cells (PBSCs) if there was a weight discrepancy more than 10kg between the donor and the recipient, or because of refusal by the donor for donation of bone marrow under general anesthesia. Among the six PBSCs donors, all were from domestic registries except in one case the donor was from the USA. The median number of infused CD34+ cells was 4.2×10^6/kg (range: 0.2～11.5). For patients who received bone marrow from the donor, the median number of infused CD34+ cells was 4.0×10^6/kg (range: 0.2～11.5), whereas it was 4.8×10^6/kg (range: 1.8～7.8) for patients who received PBSCs. In total, 31 patients received our standard TBI-containing regimen, which consisted of fractionated TBI (13.2Gy, seven fractions in 4 days) from day −7 to −4, followed by cylcophosphamide (60mg/m^2 over 30 min) on days −3, −2. Four patients received a non-TBI regimen that included busulfex (3.2mg/kg intravenously per day for 4 days) from day −7 to −4 plus cylcophosphamide (60mg/m^2 over 30 min) on days −3, −2. Between December 2005 and November 2006, we studied an additional regimen with antithymocyte globulin (thymoglobulin, Sangstat) at a dose of 1.25mg per kilogram of body weight per day on days −3, −2, in recipients who received PBSCs from mismatched unrelated donors (n=10), to prevent the development of acute GvHD together with our standard regimen, which consisted of methotrexate (10mg/m^2 intravenously bolus on day +1; and methotrexate 5mg/m^2 intravenously bolus, on days +3, +6, +11) and tacrolimus starting at day −1. In the absence of acute GvHD, tacrolimus was tapered by 25% biweekly beginning on day 120 after transplantation. For some patients (n=2), at day +11 methotrexate was not administered based on the status of the patient such as the presence of severe mucositis. G-CSF was administered in all patients at a dose of 5 μg/kg per day subcutaneously from day +7 after transplantation until neutrophil recovery. The time to hematopoietic recovery was based on the measured absolute neutrophil count (ANC) $\geq0.5\times10^9$/L and a platelet count $\geq20\times10^9$/L with the absence of platelet transfusion requirement for three consecutive days. Engraftment was assessed by routine marrow aspiration at day +21. Graft failure or aplasia was defined as the absence of haematological recovery by day +28 in patients after transplantation. Toxicity grading was assessed using the WHO criteria.[12] All patients received prophylactic antibiotics starting from day −14 until the ANC was 1.5×10^9/L. All the patients received anti-fungal prophylaxis with itraconazole from day −14 to +60 post-transplant. Pneumocystis carinii pneumonia (PCP) prophylaxis with bactrim was given throughout the conditioning, discontinued 48 h before stem cells infusion, and given from day +21 to +90. The blood components given to patients were irradiated and leukocyte-filtered before transfusion.

4. Statistical analysis

Disease-free survival (DFS) was calculated from the date of CR until the date of the first relapse after HSCT. The event-free survival (EFS) was calculated from the date of CR until recurrence or death from any cause, or on the basis of CR determined at the last follow-up after HSCT. The Kaplan-Meier method was used to calculate DFS, EFS. The statistical significance of differences with regard to various donor registries and clinical conditions was calculated using the log-rank test. The Cox model was also used

to determine which of the independent prognostic factors between groups were important in a univariate analysis. Patients still alive in CR were censored at their last follow-up. All analyses were based on a retrospective review. The last follow-up date was November 15, 2006.

RESULTS

1. Donor registries

The first unrelated donor HSCT performed in Korea was carried out in July 1996 by a donor registered with the Catholic Hematopoietic Information Bank. The first foreign donor HSCT, from Japan, for AML was performed in April 1998. The first unrelated bone marrow donor from the TCMDR was grafted in October 1998. In addition, the first unrelated HSCT from the NMDP was successful in March 2006. By November 2006, 87 donors were identified in the above registries. Among these, 35 AML patients received unrelated mismatched donor HSCT with more than a one allele mismatch as shown in Table 1.

2. Engraftment

We observed no graft failure in this study. Sustained neutrophil engraftment was reached at a median of 14 days (range 8～27) after transplant in all evaluated patients. Sustained platelet engraftment was obtained at a median of 17 days (range 11～24) in all evaluated patients.

3. GvHD

Fourteen of 33 evaluated patients (42%) developed acute GvHD with a grade I (5, 15%), grade II (7, 21%) or grade III (2, 6%) reaction; there were no grade IV cases. Chronic GvHD developed in 10/18 (56%) evaluated patients, and two of them (11%) had extensive disease. The most common single organ involved in this study was the skin in 7 or 39% of cases, and otherwise included the liver in 2 or 11%; involvement of more than 2 organs such as the skin and liver in combination was observed in 7 or 39% of cases.

4. Survival rate

The disease-free survival rate (DFS) and event-free survival rate (EFS) were as follows: the overall five-year estimated DFS of mismatched unrelated donor HSCT from multinational donor registries was about 80% (Fig. 1A) and the corresponding data for EFS was 53% (Fig. 1B). In order to compare the results of DFS and EFS from the HLA-mismatched donors around the world, we compared the survival curves for the two groups based on the donor registry; we compared the domestic donors (from two Korean donor reg-

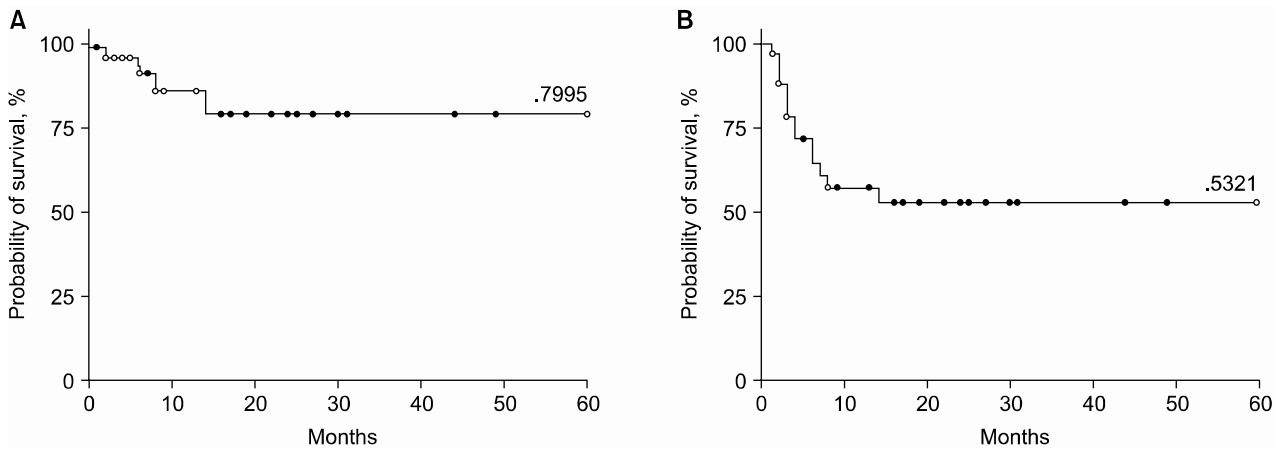

Fig. 1. Disease-free survival rate (A) and event-free survival rate (B) of mismatched unrelated donor HSCT from multinational donor registries worldwide.

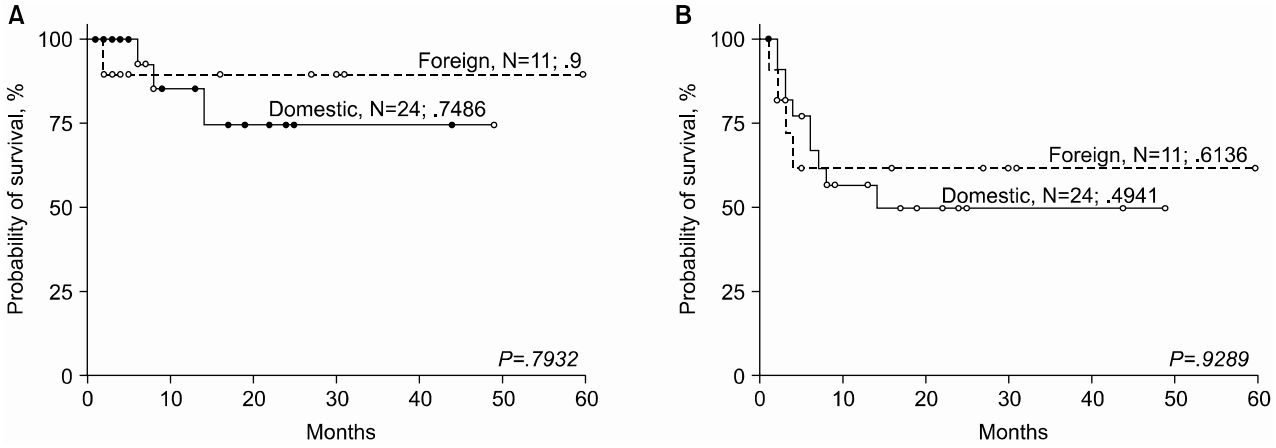

Fig. 2. Defined outcomes according to the different donor registries included. Disease-free survival rate (A) and event-free survival rate (B) of mismatched unrelated donor HSCT from multinational donor registries.

istries) with the foreign donors (from two Asian and one American registry). In contrast to the overall survival results illustrated above, there was a slightly improved DFS and EFS when we used foreign donors as shown in Fig. 2A, 2B; however, these differences were not significant.

Univariate analysis showed that the stage of disease pre-transplant, the different conditioning regimens used, and the age of the patient had a marked influence on DFS, but not on EFS after the mismatched unrelated donor HSCT. However, all other initial characteristics, shown in Table 1, in addition to the infused cell doses, CMV antigenemia status, GvHD prophylactic regimens, different veno-occlusive disease (VOD) prophylaxis, cytogenetic abnormalities were found to have no significant impact on DFS or EFS. Finally, only the TBI-based conditioning regimen showed marginal significance by multivariate analysis (P=.059).

5. Relapse and transplant-related mortality

The relapse rate was 11% (4/35) in this study. The cumulative incidence of non-relapse transplant-related mortality (TRM) was 26% (9/35). Among the six patients who had an IR or refractory status pre-transplant, two relapsed early after transplantation and another two out of 29 were in the CR group (33% vs 7%). The causes of non-relapse TRM were as follows: two cases of CMV pneumonia, one of PCP, two with thrombotic-thrombocytopenic purpura, two with severe veno-occlusive disease combined with bacterial pneumonia and two with unexplained alveolar hemorrhage combined with microbiologically unproven pneumonia. Most of these diagnoses were confirmed by appropriate laboratory testing except for the PCP pneumonia and unexplained alveolar hemorrhage. Seven out of 35 patients (20%) died within the first 100 days after HSCT and six died after 100 days as a result of the HSCT. The actuarial 21-month TRM posttransplant was 47% (C.I. 37～57).

6. Other transplant-related complications

Additional complications were observed such as one case of manageable eosinophilic pneumonia, four cases of toxic hepatitis associated with the conditioning regimen, two cases of mild VOD and one of maxillary osteomyelitis due to actinomyces infection. Fortunately, all these patients recovered after appropriate treatment.

DISCUSSION

Before 1998, Korean patients had no opportunity to receive HLA-matched donor HSCT from outside of Korea. However, our data from

this study showed a 100% engraftment rate using Japanese, Taiwanese and even American donors. These findings suggest that the use of multinational donor registries for unrelated donor HSCT in a variety of lymphohematological malignancies may be safe and effective. Recruitment of Korean donors over the last 10 years has increased the donor pool size only modestly in comparison with other countries. In our study the average time to find an appropriate unrelated donor from all registries enrolled in this study was four months. Therefore, if donors could be identified in a timely fashion, for AML patients who are categorized as high-risk for relapse, then they can receive HSCT at an optimal time specifically when they are in CR.

Our results in Korean AML patients after HLA-mismatched unrelated donor HSCT showed a 26% TRM together with an 11% relapse rate using HLA-mismatched multinational donors. There was an 80% overall five-year estimated DFS for intermediate- to high-risk AML patients and an overall 53% five-year estimated EFS; these results suggest that we can perform unrelated donor HSCT from donors listed in worldwide registries. Furthermore, improvement of patient protocols for the HSCT, continue to be needed to lower the TRM in future patients. Our findings showed a similar, or at least a trend, for greater long-term overall DFS and EFS with the foreign donors; this was surprising and may have been due to the small sample size. In addition, the incidence of acute and chronic GvHD was not different in comparisons between the domestic donors and the foreign donors. Interestingly, we noted rather paradoxically an improved DFS and EFS in patients who developed mild to moderate acute GvHD after they received ATG for GvHD prophylaxis compared to the patients who did not receive ATG (data not shown). This finding illustrated the difference in the role of acute GvHD in unrelated donor HSCT compared with chronic GvHD in their antileukemic effects. Therefore, in order to reduce the TRM using unrelated donor peripheral blood stem cells, particularly in the HLA-mismatched setting, ATG may play a critical role in immunosuppression providing survival benefits from the reduction of detrimental GvHD/rejection.[13,14)]

In addition, to investigate the allogeneic potential between HLA-mismatched unrelated stem cell donor/recipient pairs, as propsed by Elsner et al,[15)] we adopted an analytic tool using HistoCheck's databases containing HLA sequences via internet (http://www.histocheck.de.). Unfortunately, we could not find any correlation with critical TRCs, i.e. development of acute GvHD, in this study (data not shown).

In the future a comparative study in patients who receive either peripheral blood stem cells or bone marrow stem cells from HLA-mismatched multinational donors is needed to evaluate the development of GvHD and graft failure in HLA class I or II mismatches. Further study analyzing a large cohort of Korean or other Asian unrelated HSCT patients with high-risk AML patients is now necessary. With the use of different transplant and immunosuppression regimens, based on patient-risk, development of worldwide donor selection criteria may be refined to meet the needs of the individual patient.

요 약

배경: 많은 급성골수성백혈병 환자들이 그간 HLA가 일치하는 비혈연 공여자들로부터 조혈모세포이식을 받아왔다. 최근까지의 보고에 의하면 심지어는 HLA가 부적합하는 다국가 비혈연 공여자들로부터의 이식에서도 수용할 만한 이식관련 합병증과 장기생존율을 보이고 있다.

방법: 저자들은 한국(24명), 일본 골수 공여 프로그램(JMDP, 3명), 대만 주치 골수 공여 등록소(TCMDR, 6명), 서양의 국립골수공여프로그램(NMDP, 2명)을 포함하는 다국적 공여 은행을 이용한 35명의 비혈연 조혈모세포이식 결과를 보고한다.

결과: 대상 환자의 중앙 연령은 36세(범위, 16～53)이며 추적 중앙값은 21개월(범위, 5～60개월)이다. 기증 공여자의 중앙 연령은 28세(범위, 20～53)

이며 추적 중앙값은 21개월(범위, 5～60개월)이다. 대부분의 환자들은 표준 혹은 불량 예후군에 속하였다. 이식 전처치법은 주로 cyclophosphamide와 전신 방사선조사를 포함하는 방법이었고(31명) 본 센터의 표준 이식편대 숙주병 예방법인 tacrolimus와 단기간의 methotrexate 병합요법을 사용하였다. 일부 환자들에서(10명) 2일 동안의 항흉선세포 글로부린(ATG, Sangstat)을 병용하였다. 모든 환자에서 생착이 이루어졌다. 급성 이식편대 숙주병의 발생률은 42%, 만성은 56%였다. 현재까지 4명(11%)이 재발하였다. 이식 후 2년 동안의 비재발 이식관련 사망률은 26%였다. 5년 추정 무병 생존율과 무사고 생존율은 각각 80%와 53%였다.

결론: 이상의 결과들은 다국적 비혈연 공여자를 이용한 조혈모세포이식이 고위험군 한국인 급성골수성백혈병 환자들에게 선택할 만한 치료법의 하나가 될 수 있음을 제시한다.

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