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Clinical Experience of Allogeneic Hematopoietic Stem Cell Transplantation in Elderly Patients Aged 60 Years and Older in South Korea

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Purpose: The purpose of this study is to share our outcomes and experiences on allogeneic hematopoietic stem cell transplantation (HSCT) in elderly patients aged 60 years and older with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) in South Korea, and to compare them with other studies.

Materials and Methods: We analyzed the clinical outcomes of 116 patients with AML or MDS aged 60 years and older who underwent allogeneic HSCT. We also analyzed which pretreatment factors affect the overall survival (OS) after allogeneic HSCT.

Results: Neutrophil and platelet engraftment were achieved at median day +11 [interquartile range (IQR) 10–15] and +14 (IQR 11–19), respectively. A complete donor chimerism was confirmed in 65 (56.0%) patients at 3 weeks and in 63 (54.3%) patients at 3 months after HSCT. The estimated incidence of grade II–IV acute graft-versus-host disease (GVHD) at day 100 was 13.7%. The estimated incidence of chronic GVHD at 2 years was 38.8%. Within a median follow-up of 14 months after HSCT, OS was 64% at 1 year and 55% at 2 years, and non-relapse mortality (NRM) was 20% at 1 year and 28% at 2 years. Multivariate analysis revealed that male sex and Hematopoietic Cell Transplantation-Specific Comorbidity Index ≥3 were associated with poor OS.

Conclusion: This study showed that allogeneic HSCT in elderly adults aged 60 and older can be performed with successful engraftment and acceptable NRM and OS are expected given the generally known survival of patients with higher risk MDS and poor risk AML.

Key Words: Myelodysplastic syndrome, acute myeloid leukemia, hematopoietic stem cell transplantation, aged, Asia

INTRODUCTION

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are representative myeloid malignancies. There are many treatment options for MDS and AML, from best supportive care to aggressive chemotherapy. Among them, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment strategy for patients with AML or MDS. The therapeutic effect of allogeneic HSCT is thought to be largely mediated by graft-versus-leukemic (GVL) effect.

MDS and AML are known to mainly occur in the elderly, and the median age of diagnosis for both diseases is over 60 years.[1] The management of elderly patients with MDS and AML is often challenging due to their age-related non-hematologic comorbidities and increased vulnerability to therapeutic toxicities.

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Conventionally, myeloablative conditioning (MAC) regimens were administered before allogeneic HSCT to induce tumor cytoreduction and ideally disease eradication, and to achieve sufficient immunosuppression to overcome host rejections of the donor stem cells.[2] As MAC regimens resulted with high regimen-related toxicities in the elderly and patients with comorbidities, reduced intensity conditioning (RIC) regimens, which are designed to be less ablative and less toxic, were developed. Several studies showed that RIC regimens followed by allogeneic HSCT were associated with mixed chimerism and then full chimerism with a documented GVL effect in the setting of hematologic malignancies and graft-versus-tumor effect in the setting of solid tumors. RIC is thought to rely more on GVL effect and less on cytotoxic effect for therapeutic efficacy.[3] Many studies comparing MAC with RIC in patients with AML or MDS showed that RIC is associated with increased relapse but reduced treatment-related mortality, resulting in similar overall survival (OS).

Recently, Basak, et al.[4] reported a retrospective analysis of the outcomes of allogeneic HSCT in a large cohort of patients aged 65 years or older reported to the European Group for Blood and Marrow Transplantation (EBMT). Their study confirmed the feasibility of allogeneic HSCT in a large-series of elderly patients, with acceptable non-relapse mortality (NRM) and OS at 1 and 3 years, including those with very advanced age of 75 years and older.

In Asia, Aoki, et al.[5] reported a large-scale, nationwide retrospective study on the outcomes of allogeneic HSCT using RIC in AML patients, including a substantial number of elderly patients aged 60 years and older. However, there are still limited reports on the outcomes of allogeneic HSCT in elderly patients aged 60 years or older, especially in Asian patients. The purpose of the present study is to share our outcomes and experiences on allogeneic HSCT in elderly patients aged 60 years and older with MDS or AML in South Korea, and to compare them with other studies. We also analyzed which pretreatment factors affect OS after allogeneic HSCT.

MATERIALS AND METHODS

Study population

A total of 116 patients with AML or MDS aged 60 years or older who underwent allogeneic HSCT at Soonchunhyang University Bucheon Hospital and Chonnam National University Hwasun Hospital between 2011 and 2020 were included in this study. Written informed consent was obtained from all patients before transplantation. This study was approved by the Institutional Review Board of each hospital. In Soonchunhyang University Bucheon Hospital, IRB number is 2019-02-014. In Chonnam National University Hwasun Hospital, IRB number is CNUHH-2020-148. For this retrospective study, clinical data such as baseline characteristics and transplant outcomes were collected from the medical records of each hospital. Risk stratification of MDS patients was based on the revised International Prognostic Scoring System.[6] Risk stratification of AML patients was based on the 2017 European LeukemiaNet risk stratification.[7] Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) scores were calculated from the patient data.

Conditioning and transplantation

The RIC regimens were fludarabine (30 mg/m^2/day for 6 days) with 2 or 3 days of intravenous busulfan [3.2 mg/kg per day; Bu(2)/Flu or Bu(3)/Flu] or treosulfan (150 mg/m^2; Treo/Flu). The number of days of busulfan infusion was determined by the physician based on the patient's condition. The MAC regimens were 4 days of intravenous busulfan (3.2 mg/kg per day) with fludarabine [30 mg/m^2/day for 6 days; Bu(4)/Flu] or total-body irradiation (12 to 14.2 Gy), cyclophosphamide (120 mg/kg over 2 days) and fludarabine (30 mg/m^2/day for 5 days; TBI/Cy/Flu). Graft-versus-host disease (GVHD) prophylaxis was achieved through single or double administration of the following drugs; methotrexate 5 to 10 mg/m^2 on days 3, 6, and 11, cyclosporine, tacrolimus, sirolimus, and mycophenolate mofetil. T cell depletion was achieved through injection of anti-thymocyte globulin. Stem-cell sources were peripheral blood and cord blood stem cells. Supportive care, including growth factors and transfusion support, was provided per institutional guidelines.

Post-transplant outcomes and management

The day of neutrophil engraftment is defined as the first of three consecutive days of achieving a sustained peripheral blood neutrophil count of >500×10^6/L. The day of platelet engraftment is defined as the first of seven consecutive days of independence from platelet transfusion with a platelet count of more than >20×10^9/L. Chimerism status was assessed at 3 weeks and 3 months after allogeneic HSCT by using bone marrow or peripheral blood cells. Chimerism was determined by the analysis of 16 short-tandem repeats using polymerase chain reactions or capillary Electrophoresis and FISH analysis of sex chromosomes in sex-mismatched transplantation. Complete donor chimerism meant that 100% of bone marrow and blood cells are derived from the donor.

Veno-occlusive disease (VOD) was diagnosed according to the modified Seattle criteria before 2016 and the revised EBMT diagnostic criteria after 2016. International Bone Marrow Transplant Registry (IBMTR) severity index was used for grading acute GVHD.[8] OS was defined as the number of days from allogeneic HSCT until death from any cause. NRM was defined as the number of days from allogeneic HSCT to death without relapse.

Statistical analysis

OS and cumulative incidences of NRM, relapse, acute GVHD, grade 2–4 acute GVHD, and chronic GVHD were estimated us-

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ing the Kaplan-Meier method with intention-to-treat analysis, and were compared using log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to analyze the association between various pretreatment factors and OS. The chi-square test was used to evaluate the significance of the differences in crude incidences of relapse according to sex and HCT-CI and in the proportion of MDS patients between males and females. $P<0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics version 26 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of patients receiving allogeneic HSCT

Baseline characteristics of patients before allogeneic HSCT are listed in Table 1. The median age of a total of 116 patients was 64 years, of whom 46 were aged 65 years and older. The male to female ratio was 1.9:1. There were 46 MDS and 70 AML patients in our study cohort. Among them, 93.5% (43/46) of patients with MDS received hypomethylation therapy prior to transplantation, and 87.1% (61/70) of patients with AML achieved complete remission prior to transplantation. The median HCT-CI score was 2, and 48 patients had scores ≥3.

The characteristics of patients associated with allogeneic HSCT are listed in Table 2. Most (109, 94.0%) of them received RIC using busulfan or treosulfan with fludarabine, but 7 (6.0%) patients received MAC. Of the patients receiving RIC, 86 patients received busulfan at 3.2 mg/kg per day for 2 days, 15 patients received 3 days, and eight patients received treosulfan. T cell depletion with anti-thymocyte globulin was conducted in most of cases (107, 92.2%). They underwent peripheral blood (112, 96.6%) or cord blood (4, 3.4%) allogeneic HSCT from matched-related or unrelated (72, 62.1%), mismatched-related or unrelated (11, 9.5%), or haploidentical donors (29, 25.0%). Thirty-three (28.4%) patients received HSCT from related donor, and only 2 (6.1%) of them received from HLA mismatched donor. ABO disparity was present in 57 (49.1%) patients. The median count of CD34 cells infused was 4.55×10^6/kg [interquartile range (IQR) 3.1–7.58]. Thirty-eight (32.8%) patients received more than 6×10^6/kg of CD34 cells. Meanwhile, 7 (6.0%) patients received less than 2×10^6/kg of CD34 cells.

Clinical outcomes following allogeneic HSCT

Clinical outcomes following allogeneic HSCT are listed in Table 3. Neutrophil and platelet engraftment were achieved at median day +11 (IQR 10–15) and +14 (IQR 11–19), respectively, while 9 (7.8%) patients experienced primary graft failure (data not shown). A complete donor chimerism was confirmed in 65 (56.0%) patients at 3 weeks and in 63 (54.3%) patients at 3 months after HSCT. Specifically, 67.7% (44/65) of the patients with confirmed complete donor chimerism at 3 weeks maintained it at 3 months, but 32.3% (21/65) lost it at 3 months (data not shown). Conversely, in 37.3% (19/51) of patients who did not achieve complete donor chimerism at 3 weeks, it was confirmed at 3 months (data not shown).

VOD was diagnosed in 4 (3.4%) patients. Acute GVHD was observed in 32 (27.6%) patients, and the estimated cumulative incidence of acute GVHD at day 100 was 26.7% (Fig. 1A). Among them, 15 (12.9%) patients had grade II–IV acute GVHD, and the estimated cumulative incidence of grade II–IV acute GVHD at day 100 was 13.7% (Fig. 1B). Thirteen (40.6%) of patients with acute GVHD required two or more drugs for treatment of acute GVHD. Chronic GVHD was observed in 45 (38.8%) patients, and the estimated cumulative incidence of chronic GVHD at 2

Table 1. Baseline Characteristics of Patients before Allogeneic Hematopoietic Stem Cell Transplantation (n=116)

Characteristics	Value
Median age (yr)	64 (60–73)
65–69	37 (31.9)
≥70	9 (7.8)
Sex (male/female)	76/40
Diagnosis	
MDS	46 (39.7)
Hypomethylating agents	43 (93.5)
Supportive treatment	3 (6.5)
AML	70 (60.3)
2nd AML*	7 (6.0)
CR	61 (87.1)
Non-CR	9 (12.9)
Cytogenetic abnormality	44 (37.9)
Risk stratification	
MDS†	
Very good	1 (2.2)
Good	24 (52.2)
Intermediate	12 (26.1)
Poor	5 (10.9)
Very poor	4 (8.7)
AML‡	
Favorable	14 (20.0)
Intermediate	36 (51.4)
Poor	20 (28.6)
HCT-CI	
Median	2
≥3	48 (41.4)

AML, acute myeloid leukemia; CR, complete remission; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; MDS, myelodysplastic syndrome. Data are presented as n (%).
*2nd AML refers to a leukemic process either evolving from prior myelodysplasia or myeloproliferative disorder or occuring after previous exposure to radiation or chemotherapy for another cancer; †Risk stratification of MDS patients was based on the revised International Prognostic Scoring System; ‡Risk stratification of AML patients was based on the 2017 European LeukemiaNet risk stratification.

Table 2. Characteristics of Patients Associated with Allogeneic Hematopoietic Stem Cell Transplantation (n=116)

Characteristics	Value
Conditioning intensity	
RIC	109 (94.0)
Bu(2)/Flu	86 (74.1)
Bu(3)/Flu	15 (12.9)
Treo/Flu	8 (6.9)
MAC	7 (6.0)
Bu(4)/Flu	3 (2.6)
TBI/Cy/Flu	4 (3.4)
T cell depletion	107 (92.2)
Donor	
HLA matched	72 (62.1)
Related	31 (26.7)
Unrelated	41 (35.3)
HLA mismatched	11 (9.5)
Related	2 (1.7)
Unrelated	9 (7.8)
Haploidentical	29 (25.0)
Cord blood	4 (3.4)
ABO disparity	57 (49.1)
CD34 count	
Median ($\times10^6$/kg)	4.55 (IQR 3.1–7.58)
$\geq6\times10^6$/kg	38 (32.8)
$<2\times10^6$/kg	7 (6.0)

Bu(d), days of intravenous busulfan at 3.2 mg/kg per day; Cy, cyclophosphamide; Flu, fludarabine; HLA, human leukocyte antigen; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation; Treo, treosulfan; IQR, interquartile range.
Data are presented as n (%).

Table 3. Clinical Outcomes Following Allogeneic Hematopoietic Stem Cell Transplantation (n=116)

	Value
Bone marrow recovery	
ANC >500/uL	11 days (IQR 10–15)
Platelet >20000/uL	14 days (IQR 11–19)
VOD	4 (3.4)
Acute GVHD	
All grade	32 (27.6)
≥2 grade	15 (12.9)
≥2 drugs for treatment	13 (11.2)
Chronic GVHD	
All cases	45 (38.8)
Involved organs	
1	20 (17.2)
2	12 (10.3)
≥3	13 (11.2)
Lung involvement	7 (6.0)
Drugs for treatment	
1	18 (15.5)
2	20 (17.2)
≥3	7 (6.0)
Relapse	33 (28.4)
Death	52 (44.8)
NRM	26 (50.0)
Infection	3 (11.5)
GVHD±Infection	19 (73.1)
Others*	4 (15.4)

ANC, absolute neutrophil count; GVHD, graft-versus-host disease; IQR, interquartile range; NRM, non-relapse mortality; VOD, veno-occlusive disease.
Data are presented as n (%).
*Others included death from VOD; bleeding complication, such as intracranial bleeding; and thrombotic complication, such as cerebral infarction; and sudden cardiac death.

years was 38.8% (Fig. 1C). The number of organs involved in chronic GVHD was one in 20 (44.4%) patients, two in 12 (26.7%) patients, and three or more in 13 (28.9%) patients. Lung involvement of chronic GVHD was observed in 7 (15.6%) patients. The number of drugs required to manage chronic GVHD was one in 18 (40%) patients, two in 20 (44.4%) patients, and three or more in 7 (15.6%) patients.

Relapse occurred in 33 (28.4%) patients, and the estimated cumulative incidence of relapse at 2 years was 29% (Fig. 1D). The overall mortality was 44.8% (52 patients). NRM occurred in 26 (50% of deaths) patients. Specifically, GVHD with or without infection was the most common cause of NRM (73.1%, 19/26). Other causes of NRM included VOD; bleeding complication, such as intracranial bleeding; thrombotic complication, such as cerebral infarction; and sudden cardiac death.

The estimated OS and NRM are shown in Fig. 2. Within a median follow-up of 14 months (range 0.6–110.3 months) after HSCT, OS was 64% at 1 year and 55% at 2 years (Fig. 2A), and NRM was 20% at 1 year and 28% at 2 years (Fig. 2B). Specifically, the estimated OS at 2 years was 45% in MDS patients and 45.5% in AML patients, and there was no statistically significant difference (p=0.296) (Fig. 2C). The estimated NRM at 2 years was 32.9% in MDS patients and 25.5% in AML patients, and there was no statistically significant difference (p=0.809) (Fig. 2D).

Association of various pretreatment factors with OS

The association of various pretreatment factors with OS was assessed using univariate Cox proportional hazards regression analysis (Table 4). Male sex was identified to be associated with poor OS compared to female sex [hazard ratio (HR)= 2.297; 95% confidence interval (CI), 1.202–4.389; p=0.012]. In addition, HCT-CI ≥3 was identified to be associated with poor OS (HR=2.256; 95% CI, 1.301–3.911; p=0.004). HSCT from related donor was identified to be associated with better OS compared to the others (HR=0.485; 95% CI, 0.236–0.995; p=0.048). Meanwhile, HSCT from HLA-matched donors was identified to be associated with a trend towards better OS compared to the others, but not statistically significant (HR=0.629; 95% CI, 0.364–1.089; p=0.098).

In multivariate Cox proportional hazards regression analy-

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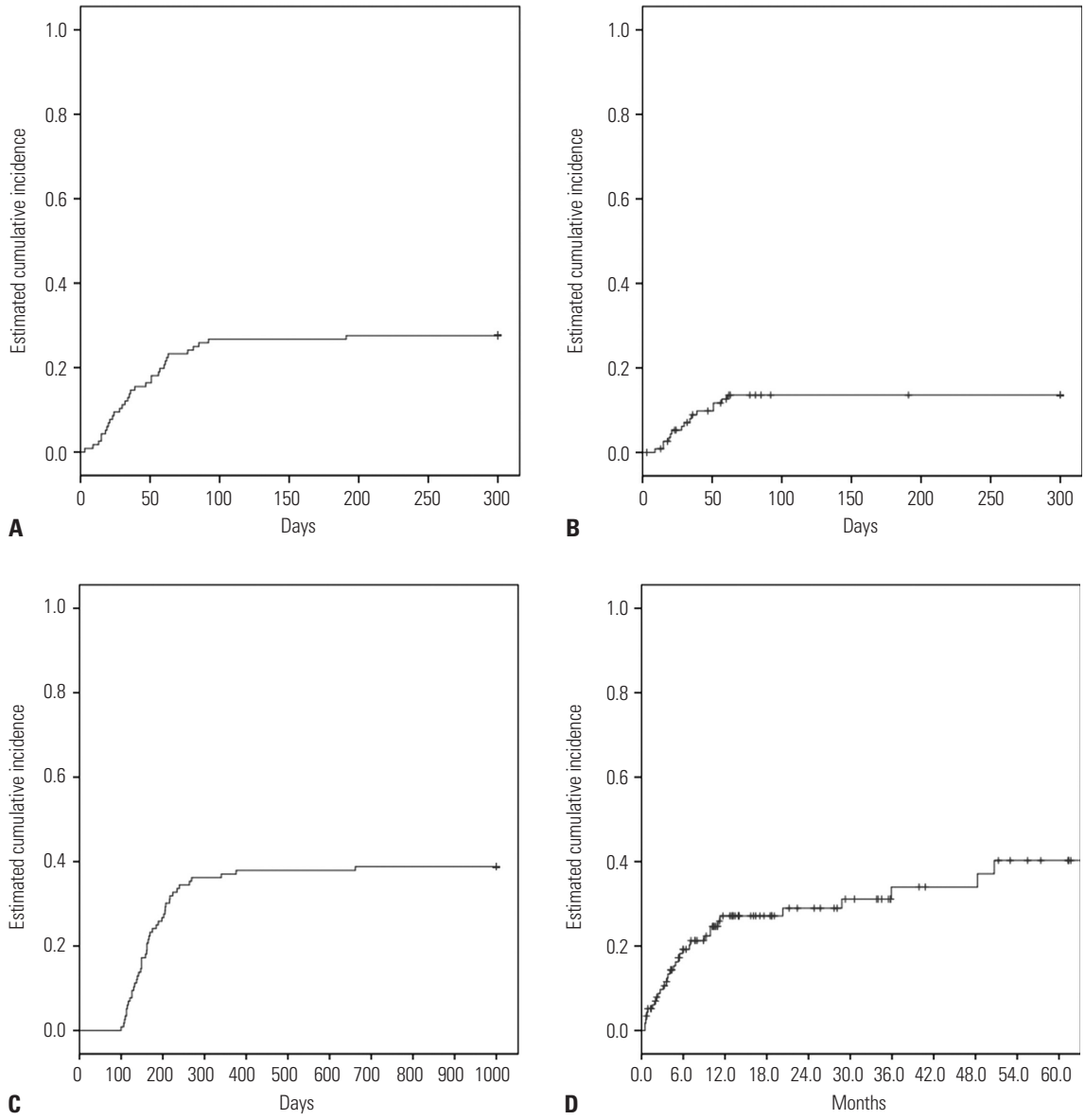

Fig. 1. Estimated cumulative incidence of GVHD and relapse. (A) Acute GVHD, all grades. (B) Acute GVHD, grade II–IV. (C) Chronic GVHD. (D) Relapse. GVHD, graft-versus-host disease.

sis, male sex and HCT-CI ≥3 were identified to be still associated with poor OS (male sex: HR=2.157; 95% CI, 1.122–4.146; p=0.021, HCT-CI ≥3: HR=2.450; 95% CI, 1.398–4.293; p=0.002). Meanwhile, the association of related donor with better OS was not statistically significant in multivariate analysis (HR=0.519; 95% CI, 0.244–1.106; p=0.089).

For the subset of male patients, NRM was 24% at 1 year and 35% at 2 years (Fig. 3A), and OS was 57% at 1 year and 45% at 2 years (Fig. 3B), which were poorer than those of female patients (p=0.075 and 0.010, respectively). For the subset of patients with HCT-CI scores ≥3, NRM was 35% at 1 year and 41% at 2 years (Fig. 3C), and OS was 47% at 1 year and 40% at 2 years (Fig. 3D), which were poorer than those of patients with HCT-CT scores <3 (p=0.008 and 0.003, respectively). There was no significant difference in the estimated cumulative incidence of relapse according to sex (p=0.465) (Fig. 3E) and HCI-CI score (p=0.495) (Fig. 3F). In addition, there was no significant difference in the crude incidence of relapse according to sex (p=0.870) and higher HCI-CI score (p=0.885) (Table 5).

DISCUSSION

Allogeneic HSCT was not actively performed in elderly patients with MDS or AML as conventional myeloablative allogeneic HSCT resulted with high regimen-related toxicities in them. However, the invention of RIC and improvements in supportive care have made it possible to safely conduct allogeneic HSCT in elderly patients. Under these circumstances, allogeneic HSCT using RIC on elderly patients has been increasingly

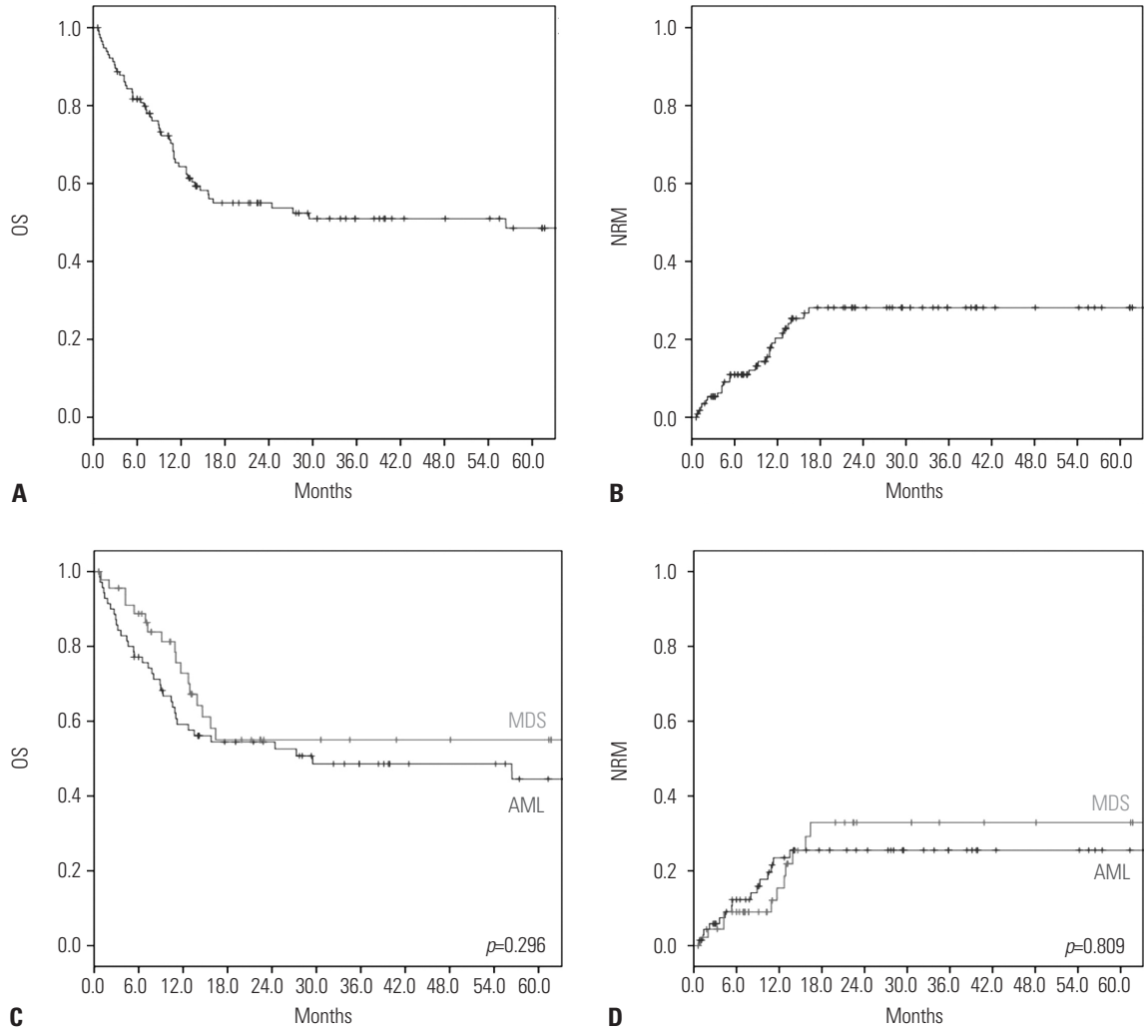

Fig. 2. OS and NRM of patients receiving allogeneic hematopoietic stem cell transplantation. (A) OS. (B) NRM. (C) OS according to type of disease. (D) NRM according to type of disease. OS, overall survival; NRM, non-relapse mortality; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

performed worldwide, and the same is true in South Korea. In this study, we analyzed the outcomes of allogeneic HSCT for 116 elderly patients aged 60 years and older with MDS or AML at two centers in South Korea, and compared them with other studies.

In the present study, neutrophil and platelet engraftment were achieved at median day +11 (IQR 10–15) and +14 (IQR 11–19), respectively. These values are similar to those generally expected when HSCT is performed using peripheral blood.[9] In addition, only 9 (7.8%) patients experienced primary graft failure (data not shown), which is comparable with the result of Basak, et al.[4] (7.8% vs. 6.0%). All patients who failed engraftment received peripheral blood stem cells infusion. Except for two patients who received 3.6 and 3.9×10^6/kg of $CD34^+$ cells, the remaining patients received 4×10^6/kg or more $CD34^+$ cells. Although we could not explain the exact cause of graft failure in all individual patients, it is thought that various factors may have been involved in the graft failure. A complete donor chimerism was confirmed in 56.0% patients at 3 weeks and in 54.3% of patients at 3 months after HSCT. These values are similar to those reported in previous papers on allogeneic HSCT using RIC.[10,11] These results suggest that there might be no particular problem in the engraftment in allogeneic HSCT with RIC in the elderly.

The estimated cumulative incidence of grade II–IV acute GVHD at day 100 was 13.7% in our study, which is slightly lower than the result of Basak, et al.[4] (13.7% vs. 28%). This difference is thought to be related to the difference in the implementation rate of T cell depletion for GVHD prophylaxis. T cell depletion was performed in 92.2% of patients in our study, but only in 66% of patients in the study of Basak, et al.[4] The estimated cumulative incidence of grade II–IV acute GVHD at day 100 observed in our study was not higher than that reported in other papers on allogeneic HSCT using RIC.[12,13] In the study by Aoki, et al.[5] on Japanese patients with AML who received allogeneic HSCT with RIC, the incidence of grade II–IV acute GVHD was 37.6% in patients aged 60–64 years and 31.0% in patients aged ≥65 years, and was not significantly different

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Table 4. Association of Various Pretreatment Factors with Overall Survival

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value*	Hazard ratio (95% CI)	*p* value*
Age ≥65 years	1.424 (0.822–2.466)	0.208		
Male (vs. Female)†	2.297 (1.202–4.389)	0.012	2.157 (1.122–4.146)	0.021
HCT-CI ≥3†	2.256 (1.301–3.911)	0.004	2.450 (1.398–4.293)	0.002
AML (vs. MDS)	1.360 (0.762–2.429)	0.299		
Cytogenetic abnormality	1.392 (0.805–2.408)	0.236		
Related donor (vs. Others)	0.485 (0.236–0.995)	0.048	0.519 (0.244–1.106)	0.089
HLA matched (vs. Others)	0.629 (0.364–1.089)	0.098	0.667 (0.375–1.186)	0.168
CD34 ≥6×10^6/kg	1.247 (0.712–2.186)	0.440		

AML, acute myeloid leukemia; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; HLA, human leukocyte antigen; MDS, myelodysplastic syndrome; CI, confidence interval.
*p-value was calculated via univariate and multivariate Cox proportional hazards regression analyses; †Statistically significant variables.

among the four age groups (50–54, 55–59, 60–64, and ≥65 years).

The estimated cumulative incidence of chronic GVHD at 2 years was 38.8% in our study, which is comparable to the incidence of chronic GVHD in patients aged 60–64 years (39.6%) and in patients aged ≥65 years (38.0%) reported in the study by Aoki, et al.[5] The estimated cumulative incidence of chronic GVHD at 2 years in our study was also not higher than that reported in other papers on allogeneic HSCT using RIC.[12,13] Indeed, Aoki, et al.[5] reported that the incidence of chronic GVHD was not significantly different among the four age groups (50–54, 55–59, 60–64, and ≥65 years).

The NRM and OS at 1 year in our study were similar to those reported by Basak, et al.[4] (20% vs. 27% for NRM and 64% vs. 56.6% for OS). In a meta-analysis performed by Rashidi, et al.[14] on allogeneic HSCT in AML patients over 60 years of age, the estimated NRM was 26% at 1 year and 29% at 2 years, and estimated OS was 58% at 1 year and 45% at 2 years. In the study of Pohlen, et al.[15] on patients aged ≥60 years with AML and MDS who received allogeneic HSCT, NRM at 1 year was 37% and OS at 3 years was 35%. In the study of Aoki, et al.,[5] the 3-year cumulative incidence of NRM was 29.2% in patients aged 60–64 years and 27.6% in patients aged ≥65 years, and was not significantly different among the four age groups (50–54, 55–59, 60–64, and ≥ 65 years).

Subgroup analysis in our study showed that male sex and HCT-CT ≥3 were independent risk factors for poor OS, and patients aged ≥65 years did not show significantly worse OS compared to those aged 60–64 years. The differences in OS according to sex and higher HCI-CI score was thought to be due to differences in the incidence of NRM, as there was no significant difference in the incidence of relapse according to sex and HCI-CI score. Pohlen, et al.[15] reported that there was no significant difference in OS between patients aged 60–64 years and ≥65 years. Interestingly, in this study, HCT-CI ≥3 was predictive for worse OS only in patients aged ≥65 years, but not in patients aged 60–64 years. Aoki, et al.[5] reported that OS was not significantly different among four age groups (50–54, 55–59, 60–64, and ≥65 years). Aoki, et al.[5] also reported that HCT-CI ≥3 was an independent prognostic factor for poor OS. Meanwhile, Basak, et al.[4] reported that patients aged ≥70 years showed slightly, but significantly poor OS compared to patients aged 65–69 years.

At present, it has not been clearly established whether male sex is a risk factor for post-HSCT mortality. However, some studies have reported that male recipients have poor post-transplantation survival compared to female recipients regardless of the donor's sex. Representatively, Kim, et al.[16] reported that male recipients had more chronic GVHD when they received stem cells from female donors and had more relapse when they received it from male donors. In our study, men tended to have more MDS diagnoses than women, but the difference was not statistically significant (male, 35/76, 46.1% vs. female, 11/40, 27.5%, p=0.052, data not shown). There was also no significant difference between male and female in other factors that could affect survival, such as age, high risk based on HCT-CI, 2 or higher grade acute GVHD, or chronic GVHD (data not shown). Based on our results, we could not explain why men had a higher mortality rate compared to female.

Given the expected NRM and OS of the elderly patients receiving allogeneic HSCT for MDS and AML, how should allogeneic HSCT be applied to which patients? In MDS, allogeneic HSCT is generally considered for patients with higher risk disease or those who failed to hypomethylating agents. As patients with higher risk MDS generally have a shorter life expectancy, allogeneic HSCT should be considered. Meanwhile, a cautious approach to transplantation is required in patients who failed to hypomethylating agents. In the study by Jabbour, et al.,[17] the 1-year OS of patients who had low-risk and intermediate-1-risk MDS at the time of HMA failure was 90% and 77%, respectively. In these patients, especially the elderly, allogeneic HSCT may not be beneficial in that the expected NRM at 1 year is about 20%. In AML, allogeneic HSCT is generally considered in patients with unfavorable prognostic disease or relapse/refractory disease, as they generally have a shorter life expectancy. However, not all of these patients, especially the elderly with comorbidities, are expected to benefit

from allogeneic HSCT. In our study, the expected NRM and OS at 1 year after allogeneic HSCT in patients aged ≥60 years with HCT-CI ≥3 were 35% and 47%, respectively. Based on these results, a cautious approach to transplantation in elderly patients with HCT-CI ≥3 is required. In patients aged ≥70 years, allogeneic HSCT should be determined in consideration of the

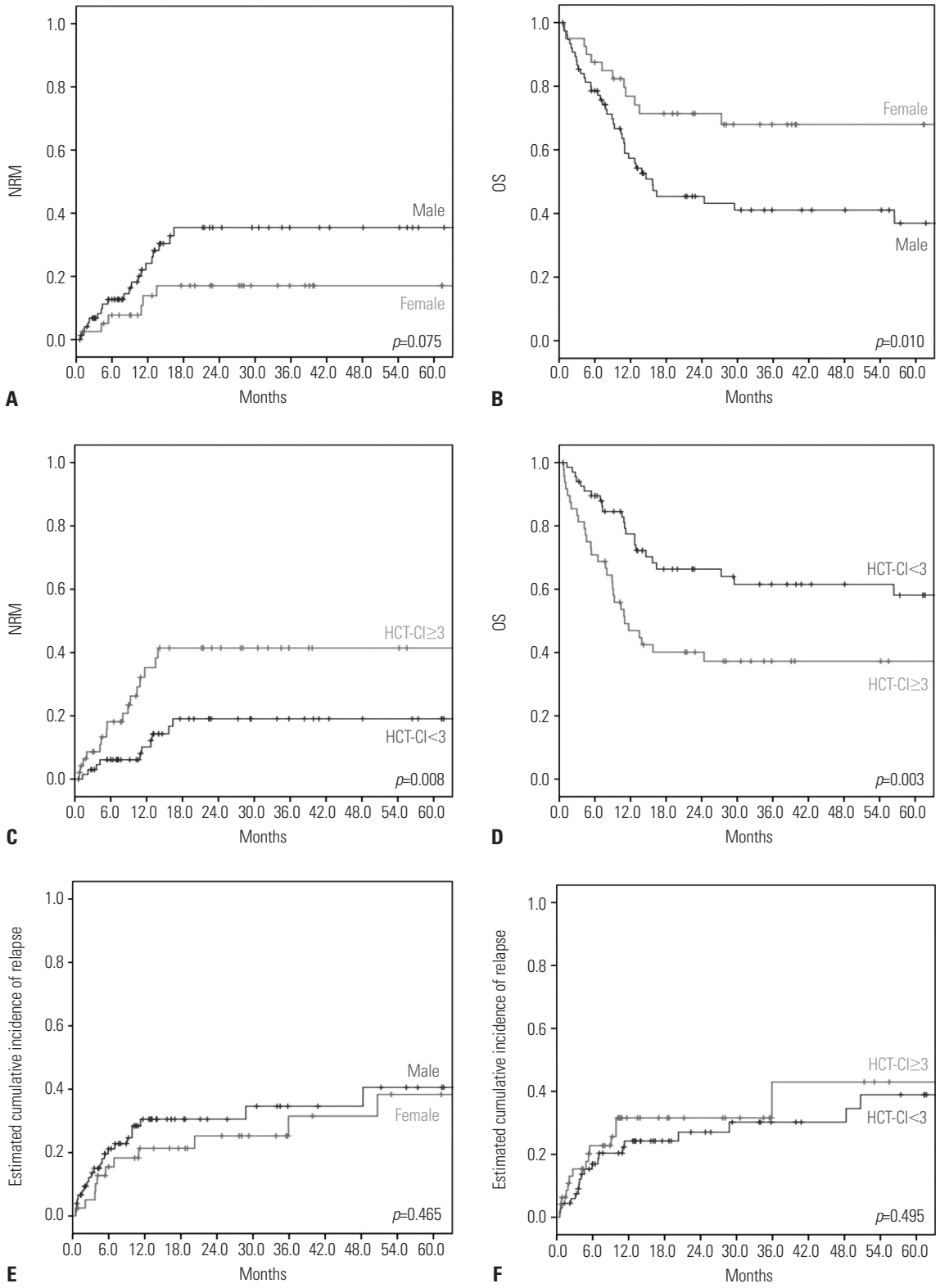

Fig. 3. NRM and OS according to sex and HCT-CI. (A) NRM according to sex. (B) OS according to sex. (C) NRM according to HCT-CI. (D) OS according to HCT-CI. (E) Estimated cumulative incidence of relapse according to sex. (F) Estimated cumulative incidence of relapse according to HCT-CI. OS, overall survival; NRM, non-relapse mortality; HCT-CI, hematopoietic cell transplantation-specific comorbidity index.

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Table 5. Crude Incidence of Relapse according to Sex and HCT-CI

	Relapse	*p* value*
Sex		0.870
Male	28.9% (22/76)	
Female	27.5% (11/40)	
HCT-CI		0.885
HCT-CI ≥3	29.2% (14/48)	
HCT-CI <3	27.9% (19/68)	

HCT-CI, hematopoietic cell transplantation-specific comorbidity index.
*p-value was calculated using chi-square test.

patient's medical conditions, such as comorbidities. Indeed, Lachowiez, et al.[18] reported that allogeneic HSCT was beneficial in terms of OS in selected patients aged ≥70 years with high-risk MDS and AML. Meanwhile, HSCT using MAC should be considered first for patients who are in good general condition, even if they are aged over 60 years. Scott, et al.[19] reported that OS was significantly better in patients with AML and MDS who received MAC compared to those who received RIC due to the significantly higher earlier relapse rates in patients who received RIC. In this paper, the 4-year relapse rate was 19.8% (95% CI, 12.7–27.9) for MAC versus 60.7% (95% CI, 51.2–69.8) for RIC. An analysis of our data on patients who received HSCT for higher risk MDS and AML showed that the relapse rate in patients aged under 60 years who received HSCT with MA was 21.3% (data not shown), which was slightly lower than the 28.4% in patients aged 60 years and older who received HSCT identified in this study.

The present study showed that allogeneic HSCT in elderly adults aged 60 years and older can be performed with successful engraftment, and acceptable NRM and OS are expected given the generally known survival of patients with higher risk MDS and poor risk AML. With careful patient selection and appropriate use of RIC, it is thought that allogeneic HSCT can be actively applied to elderly patients.

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