ORIGINAL ARTICLE

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Clinical impact of anti-thymocyte globulin on survival and graft-versus-host disease in patients undergoing human leukocyte antigen mismatched allogeneic stem cell transplantation

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Background/Aims: Rabbit anti-thymocyte globulin (ATG) is usually incorporated in hematopoietic stem cell transplantation (HSCT) to reduce the incidence of graft-versus-host disease (GVHD). This study aimed to find optimal ATG doses in patients undergoing human leukocyte antigen (HLA)-mismatched allogeneic HSCT.

Methods: We retrospectively collected medical records from 352 consecutive patients with acute myeloid leukemia (n = 214), acute lymphoblastic leukemia (n = 62), or myelodysplastic syndrome (n = 76) in eight centers of Korea between 2005 and 2015. All patients received busulfan-based conditioning without total body irradiation (TBI) and received stem cells from HLA-mismatched donors.

Results: In the current study, 5-year overall survival rates of patients receiving low to medium doses of ATG (2.5 to 7.5 mg/kg) were higher than those receiving other doses of ATG (hazard ratio [HR], 0.528; 95% confidence interval [CI], 0.311 to 0.897; $p = 0.018$). The incidence rates of extensive chronic GVHD (ecGVHD) after administration of low to medium doses of ATG were lower than those after other doses of ATG (HR, 0.447; 95% CI, 0.224 ton 0.889; $p = 0.022$).

Conclusions: The low to medium doses of ATG may be associated with improving survival outcomes and reducing incidence of ecGVHD without enhancing the chances of relapse in patients with acute leukemia or myelodysplastic syndrome undergoing non-TBI-based HLA-mismatched allogeneic HSCT.

Keywords: Antithymocyte globulin; Graft vs host disease; Survival; Human leukocyte antigen mismatch; Allogeneic hematopoietic stem cell transplantation

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative modality for treating hematologic malignancies [1]. Previously, when histocompatibility antigens were difficult to identify, allogeneic HSCT was fatal [2]. HSCT from mismatched unrelated or haploidentical family donors usually increased the risk of graft-versus-host disease (GVHD) and transplant-related

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mortality (TRM) [3]. Anti-thymocyte globulin (ATG) is used to prevent GVHD and has improved survival rates by decreasing the incidence of GVHD [4]. Over the past several decades, the use of ATG has contributed significantly in improving the outcomes of alternative donor transplantation [5]. ATG, however, may also contribute to the risk of relapse and infections, as well as of early TRM [3]. Higher doses (8 mg/kg or more) of ATG can increase the risk of relapse and decrease relapse free survival after reduced intensity conditioning (RIC) HSCT with unrelated donors [6]. There have been some retrospective trials to address the true effects of ATG on the outcome and to determine its optimal dose on the basis of human leukocyte antigen (HLA) disparity [7,8]. A recent study reported that ATG at a dose lower than 6 mg/kg was sufficient to prevent GVHD [9]. Another study recommended 4.5 to 5 and 7.5 mg/kg ATG under identical sibling donor and unrelated donor settings, respectively [10]. Therefore, we aimed to investigate the effects of different ATG doses on survival outcome and acute GVHD (aGVHD) and chronic GVHD (cGVHD) incidence in HLA-mismatched HSCT receiving busulfan-based conditioning regimen.

METHODS

Patients

This study was performed retrospectively in eight hospitals of South Korea from 2005 to 2015. In total, 352 patients suffering from acute leukemia or myelodysplastic syndrome (MDS) who underwent HSCT from HLA-mismatched unrelated or haploidentical family donors were included in the study. All patients received busulfan-based conditioning regimen, including busulfan plus cyclophosphamide or busulfan plus fludarabine. Patients who had been treated using total body irradiation (TBI)-based conditioning regimens were not included in this study. The pre-transplant disease status was divided into first or second complete remission (CR1 or CR2), refractory or relapsed, and untreated status. The definition of CR followed the recommended criteria [11]. To evaluate the degree of HLA matching, HLA A, B, C, and DR were identified using polymerase chain reaction with sequence specific primer followed by high-resolution typing, and the degree of HLA matching was classified as 1 antigen mismatch, 2 antigen mismatches, 3 antigen mismatches, and 4 antigen mismatches. Stem cell sources, such as bone marrow or peripheral blood were identified and CD34+ cell counts ($\times 10^6$/kg) were measured to evaluate the amount of stem cells. This study was approved by Institutional Review Board (IRB) of Kosin University Gospel Hospital (approval number 201809011) and the IRBs granted a waiver of informed consent because this study was a retrospective analysis that involved no more than minimal risk for patients.

Transplantation procedure

Busulfan and fludarabine (BuFlu) or busulfan and cyclophosphamide (BuCy) were used as conditioning regimens, including Bu4Cy (busulfan [3.2 mg/kg] for 4 days along with cyclophosphamide [60 mg/kg] for 2 days), Bu4Flu (busulfan [3.2 mg/kg] for 4 days along with fludarabine [30 mg/kg] for 6 days), Bu3Flu (busulfan [3.2 mg/kg] for 3 days along with fludarabine [30 mg/kg] for 6 days), Bu2Flu (busulfan [3.2 mg/kg] for 2 days along with fludarabine [30 mg/kg] for 6 days), and Bu1Flu (busulfan [3.2 mg/kg] for 1 day along with fludarabine [30 mg/kg] for 6 days). Bu4Cy and Bu4Flu were defined as myeloablative conditioning (MAC), and Bu3Flu, Bu2Flu, and Bu1Flu were defined as RIC. Rabbit ATG (thymoglobulin, Sanofi-Aventis, Cambridge, MA, USA) was administered to all patients at various dosages to prevent GVHD. We classified patients who did not receive ATG as no ATG group (0 mg/kg) and those who received 2.5 to 7.5 mg/kg (less than 8 mg/kg) as low to medium ATG group. Patients who received 9 to 12 mg/kg ATG were classified as high ATG group. ATG was given as an equally divided dose for 2 or 3 days from day –3. All patients received calcineurin inhibitors, including cyclosporine or tacrolimus with or without short-term methotrexate, as immunosuppressants to prevent GVHD.

Statistical analysis

Survival probabilities were estimated using the Kaplan-Meier method and differences in survival distributions were compared using the log-rank test. Overall survival (OS) rates were calculated from the time of HSCT to the date of death or last follow-up. Event-free survival (EFS) rates were defined from the time of HSCT to the date of relapse, progression, graft failure, donor lymphocyte infusion, or death from any cause. To identi-

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fy factors affecting OS and EFS, the log rank test and Cox proportional hazard model were used in univariate and multivariate analysis, respectively. ATG dose and other variables having $p < 0.05$ in the univariate analysis were included for multivariate analysis. We included ATG doses as a variable in multivariate analysis to validate the clinical impact of ATG dose on survival outcomes and GVHD incidence, although there were no significant differences with respect to ATG doses in univariate analysis. Consensus grading criteria was used to assess the degree of aGVHD [12]. The cumulative incidence rate (CIR) of aGVHD was calculated through day 100. A cGVHD was assessed using the traditional grading criteria [13]. For all analyses, the p values were two-sided, and $p < 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS version 24.0 software (IBM Corp., Armonk, NY, USA).

The CIR of relapse and GVHD were generated using confidence interval (CI) estimates adjusting for competing risks and compared by Gray's method. For the analysis of CIR of relapse, patients who were alive without relapse were censored.

RESULTS

Patient characteristics

This study enrolled patients with acute leukemia or MDS who underwent HLA-mismatched HSCT. Their baseline characteristics are summarized in Table 1. The median age was 46 years (range, 15 to 75). Two hundred and nine patients were diagnosed with acute myeloid leukemia (AML, 59.4%), 62 patients with acute lymphoblastic leukemia (ALL, 17.6%), five patients had mixed phenotype acute leukemia (MPAL, 1.4%), and 76 patients were diagnosed with MDS (21.6%). Of these 352 patients, 172 patients (48.8%) were confirmed as CR1 status, 29 patients (8.2%) as CR2 or subsequent remission, 55 patients (15.6%) as refractory, 34 (9.7%) as relapse, and 62 patients (17.6%) as untreated before HSCT. Of all recruited patients, 264 patients (75.0%) received RIC while 88 patients (25.0%) received MAC for conditioning. One hundred and seventy-one patients (48.6%) received stem cells from haploidentical donors and 181 patients (51.4%) from HLA-mismatched unrelated donors. HLA 1 locus mismatch was detected in 107 patients (30.4%), 2 mis-

Table 1. Baseline characteristics

Parameter	All patients (n = 352)
Age, yr	46 (15–75)
Sex	
Male	210 (59.7)
Female	142 (40.3)
Diagnosis	
AML	209 (59.4)
ALL	62 (17.6)
MPAL	5 (1.4)
MDS	76 (21.6)
Disease status	
CR1	172 (48.8)
≥ CR2	29 (8.2)
Refractory/Relapse	89 (25.4)
Untreated	62 (17.6)
Intensity of conditioning	
MAC	88 (25.0)
RIC	264 (75.0)
ATG dose, mg/kg	
0	43 (12.2)
2.5–7.5	60 (17.0)
9.0	192 (54.5)
12.0	57 (16.2)
Type of donors	
Related	171 (48.6)
Unrelated	181 (51.4)
HLA match (A,B,C, and DR), allelic level	
1 mismatch	107 (30.4)
2 mismatch	53 (15.1)
3 mismatch	39 (11.1)
4 mismatch	153 (43.5)
Stem cell source	
Bone marrow	93 (26.4)
Peripheral blood stem cell	259 (73.6)
CD34+ cell dose, $\times 10^6$/kg	6.15 (0.230–38.33)
Donor age, yr	30 (3–70)
Donor sex	
Male	235 (66.8)
Female	112 (31.8)

Values are presented as median (range) or number (%).
AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MPAL, mixed phenotype acute leukemia; MDS, myelodysplastic syndrome; CR, complete remission; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; ATG, anti-thymocyte globulin; HLA, human leukocyte antigen.

matches in 53 patients (15.1%), 3 mismatches in 39 patients (11.1%), and 4 mismatches in 153 patients (43.5%). Among the patients who received stem cells from mismatched family donors, 161 patients (94.2%) had HLA 3 or 4 mismatches, and among those who received from unrelated donors, 31 patients (17.1%) had HLA 3 or 4 mismatches. Forty-three patients (12.2%) did not receive ATG during transplantation, 60 patients (17.0%) were treated with 2.5 to 7.5 mg/kg of ATG, 192 patients (54.5%) with 9.0 mg/kg of ATG, and 57 patients (16.2%) with 12.0 mg/kg of ATG.

Prognostic factors for OS, EFS, and relapse

In univariate analysis, there were significant differences in 5-year OS rates according to disease status (39.1% in CR1, 54.0% in ≥ CR2, 11.5% in relapse/refractory, and 38.8% in untreated status, $p < 0.001$). In addition, conditioning intensity had significant impact on OS (18.2% in MAC group vs. 36.3% in RIC group, $p = 0.026$). However, there was no significant difference in 5-year OS according to the other clinical factors: sex (male 30.3% and female 34.8%, $p = 0.842$), age (< 50 years 37.8% and ≥ 50 years 24.3%, $p = 0.096$), diagnosis (AML 30.1%, ALL 34.1%, MPAL 53.3%, and MDS 40.1%, $p = 0.829$), HLA mismatch (1 mismatch 30.8%, 2 mismatches 44.8%, 3 mismatches 23.2%, and 4 mismatches 32.9%, $p = 0.326$), stem cell source (bone marrow 34.8% and peripheral blood 33.5%, $p = 0.238$), CD34+ cell dose (< 2.0 × 10^6/kg 51.4% and ≥ 2.0 × 10^6/kg 32.1%, $p = 0.40$), and median donor age (< 30 years 36.0%, 30 to 49 years 32.3%, and ≥ 50 years 20.1%, $p = 0.067$). There were significant differences in the 5-year EFS based on disease status (38.7% for CR1, 44.5% for ≥ CR2, 9.4% for relapse/refractory, and 33.6% for untreated status, $p < 0.001$) and median donor age (< 30 years 37.0%, 30 to 49 years 26.3%, and ≥ 50 years 17.8%, $p = 0.010$). However, there was no significant difference in EFS on the basis of other clinical factors, including sex (male 28.9% and female 31.2%, $p = 0.97$), patient's age (< 50 years 34.6% and ≥ 50 years 23.6%, $p = 0.364$), diagnosis (AML 28.1%, ALL 37.3%, MPAL 30.0%, and MDS 35.2%, $p = 0.299$), conditioning intensity (MAC 25.3% and RIC 32.6%, $p = 0.132$), HLA mismatch (1 mismatch 32.5%, 2 mismatches 38.5%, 3 mismatches 17.6%, and 4 mismatches 28.1%, $p = 0.174$), stem cell source (bone marrow 29.8% and peripheral blood 32.3%, $p = 0.168$), and CD34+ cell dose (< 2.0 × 10^6/kg 39.3% and ≥ 2.0 × 10^6/kg 30.5%, $p = 0.886$). The 5-year CIR of relapse, relapsed or refractory disease status at the time of HSCT was significantly associated with higher relapse compared to CR or untreated status (83.2% in relapse/refractory vs. 39.3% in CR1, 48.2% in ≥ CR2, and 30.4% in untreated status, $p < 0.001$). However, there was no significant association between CIR of relapse and other clinical factors, such as sex (male 51.4% and female 48.9%, $p = 0.906$), age (< 50 years 49.3% and ≥ 50 years 49.4%, $p = 0.868$), conditioning intensity (MAC 50.4% and RIC 49.3%, $p = 0.958$), stem cell source (bone marrow 48.6% and peripheral blood 48.6%, $p = 0.402$), CD34+ cell dose (< 2.0 × 10^6/kg 50.9% and ≥ 2.0 × 10^6/kg 49.3%, $p = 0.532$), and median donor age (< 30 years 46.9%, 30 to 49 years 51.4%, and ≥ 50 years 55.3%, $p = 0.614$). However, three ATG groups did not show significant differences in their 5-year OS (30.7% in no ATG group, 46.2% in low to medium dose ATG group, and 32.2% in high dose ATG group, $p = 0.615$) and, 5-year EFS (37.6% in no ATG group, 41.5% in low to medium dose ATG group, and 29.0% in high dose ATG group, respectively; $p = 0.289$). In addition, there was also no significant difference in 5-year CIR of relapse among the three ATG groups (39.9% in no ATG group, 42.1% in low to medium dose ATG group, and 51.4% in high dose ATG group, respectively; $p = 0.289$).

Prognostic factors for grade 2 to 4 aGVHD and extensive chronic GVHD

In univariate analysis, three ATG groups did not significantly affect the CIR of grade 2 to 4 aGVHD. However, the low to medium ATG group tended to show lower incidence rate of grade 2 to 4 aGVHD than those of other two groups (29.6% in low to medium ATG vs. 46.3% in no ATG group and 34.5% in high ATG group, $p = 0.083$) although the difference was not statistically significant. Age and conditioning intensity significantly affected grade 2 to 4 aGVHD incidence; age (< 50 years 38.6% and ≥ 50 years 29.9%, $p = 0.018$) and conditioning intensity (MAC 48.4% and RIC 30.8%, $p = 0.003$). However, there was no significant association between grade 2 to 4 aGVHD incidence and other clinical factors, including sex (35.2% in male and 34.8% in female, $p = 0.907$), disease status (31.6% in CR1, 21.4% in ≥ CR2, 47.4% in untreated, and 37.9% in refractory/relapse status, $p = 0.05$), stem cell source (42.3% for bone marrow and 32.6% for peripheral blood, $p = 0.211$), CD34+ cell dose (35.7 % in < 2.0 ×

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Table 2. Multivariate analysis of the 5-year OS rates, the 5-year EFS rates, and the 5-year cumulative incidence rates of relapse in patients with acute leukemia and myelodysplastic syndrome

Parameter	5-yr OS		5-yr EFS		5-yr cumulative incidence of relapse	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Total ATG dose, mg/kg						
0	1		1		1	
2.5–7.5	0.528 (0.311–0.897)	0.018	0.792 (0.496–1.263)	0.327	0.580 (0.300–1.122)	0.105
9–12	0.716 (0.465–1.101)	0.128	0.902 (0.612–1.329)	0.602	0.936 (0.575–1.521)	0.789
Disease status						
CR1	1		1		1	
≥ CR2	0.718 (0.379–1.360)	0.309	0.997 (0.580–1.713)	0.992	1.152 (0.614–2.161)	0.001
Refractory/Relapse	2.903 (2.101–4.009)	< 0.001	2.803 (2.036–3.858)	< 0.001	1.726 (0.787–3.787)	0.038
Untreated	1.290 (0.849–1.960)	0.232	1.275 (0.862–1.886)	0.224	4.964 (2.692–9.152)	< 0.001
Conditioning intensity						
MAC	1					
RIC	2.051 (1.404–2.996)	< 0.001				
Age of donor, yr						
< 30			1			
30–49			1.293 (0.975–1.716)	0.075		
≥ 50			1.328 (0.807–2.185)	0.264		

OS, overall survival; EFS, event-free survival; HR, hazards ratio; CI, confidence interval; ATG, anti-thymocyte globulin; CR, complete remission; MAC, myeloablative conditioning; RIC, reduced intensity conditioning.

10^6/kg and 35.2% in ≥ 2.0 × 10^6/kg, $p = 0.76$), and median donor age (33.7% in < 30 years, 33.6% in 30 to 49 years, and 46.8% in ≥ 50 years, $p = 0.316$). However, the CIR of extensive chronic GVHD (ecGVHD) significantly varied among ATG groups (62.1% in no ATG, 27.1% in low to medium ATG, and 36.1% in high ATG group, $p = 0.012$). With respect to the stem cell source, patients receiving peripheral blood stem cells showed significantly higher ecGVHD rate compared to those receiving bone marrow stem cell (44.2% vs. 22.1%, respectively; $p < 0.001$). However, there was no significant association between ecGVHD incidence and other factors, such as age (42.1% in < 50 years and 34.8% in ≥ 50 years, $p = 0.42$), disease status (35.5% in CR1, 37.7% in ≥ CR2, 37.9% in untreated, and 69.0% in refractory/relapse status, $p = 0.58$), conditioning intensity (70.5% in MAC and 35.5% in RIC, $p = 0.557$), HLA mismatch (54.2% in 1 mismatch, 23.8% in 2 mismatches, 40.7% in 3 mismatches, and 31.9% in 4 mismatches, $p = 0.469$), CD34+ cell dose (54.1% in < 2.0 × 10^6/kg, and 38.7% in ≥ 2.0 × 10^6/kg, $p = 0.071$), and median donor age (34.3% in < 30 years, 45.4% in 30 to 49 years, and 28.3% in ≥ 50 years, $p = 0.852$).

Multivariate analysis for OS, EFS, relapse, aGVHD, and ecGVHD

The factors affecting the 5-year OS and 5-year EFS in multivariate analysis are shown in Table 2. The low to medium ATG group showed significantly longer survival compared with other ATG group (hazard ratio [HR], 0.528; 95% CI, 0.311 to 0.897; $p = 0.018$) (Fig. 1A). Moreover, the 5-year OS of patients conditioned with RIC and with disease status of refractory/relapse was lower than that of patients conditioned with MAC and with disease status of CR1, respectively ([HR, 2.051; 95% CI, 1.404 to 2.996; $p < 0.001$] and [HR, 2.903; 95% CI, 2.101 to 4.009; $p < 0.001$]). The 5-year EFS of patients with disease status of refractory/relapse was significantly lower than that of patients with disease status of CR1 (HR, 2.803; 95% CI, 2.036 to 3.858; $p < 0.001$). But there was no significant association between the 5-year EFS with ATG dose

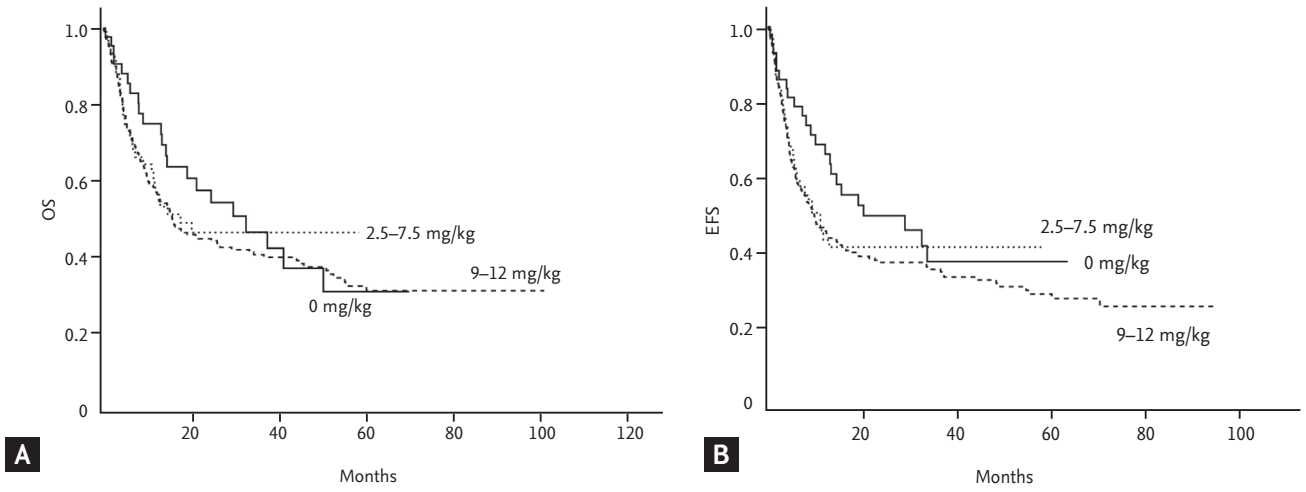

Figure 1. (A) The 5-year overall survival rates (OS) of the three anti-thymocyte globulin (ATG) groups (0, 2.5 to 7.5, and 9 to 12 mg/kg). (B) The 5-year event-free survival rates (EFS) of the three ATG groups.

Table 3. Multivariate analysis of grade 2-4 acute GVHD and extensive chronic GVHD in patients with acute leukemia and myelodysplastic syndrome

Parameter	Grade 2–4 acute GVHD		Extensive chronic GVHD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Total ATG dose, mg/kg				
0	1		1	
2.5–7.5	0.908 (0.490–1.681)	0.759	0.447 (0.224–0.889)	0.022
9–12	0.533 (0.287–0.992)	0.047	0.678 (0.442–1.038)	0.074
Age of patient, yr				
< 50	1			
≥ 50	1.519 (1.012–2.278)	0.044		
Conditioning intensity				
MAC	1			
RIC	2.140 (1.299–3.524)	0.003		
Stem cell source				
Bone marrow			1	
Peripheral blood stem cell			0.887 (0.572–1.375)	0.591

GVHD, graft-versus-host disease; HR, hazards ratio; CI, confidence interval; ATG, anti-thymocyte globulin; MAC, myeloablative conditioning; RIC, reduced intensity conditioning.

(HR, 0.792; 95% CI, 0.496 to 1.263; $p = 0.327$) (Fig. 1B). The 5-year CIR of relapse for low to medium ATG group was higher than those of other ATG groups (HR, 0.580; 95% CI, 0.300 to 1.122; $p = 0.105$) but the 5-year CIR of relapse of patients with disease status of CR1 was lower compared to patients with other disease statuses (Table 2). The results of multivariate analysis for CIR of GVHD are described in Table 3. The CIR of grade 2 to 4 aGVHD was significantly lower in high ATG group than that in other ATG groups (HR, 0.533; 95% CI, 0.287 to 0.992; $p = 0.047$) (Fig. 2A). However, the CIR of grade 2 to 4 aGVHD was significantly higher for patients of older age (50 years or more) and conditioned with RIC than that of patients less than 50 years old and conditioned with MAC, respec-

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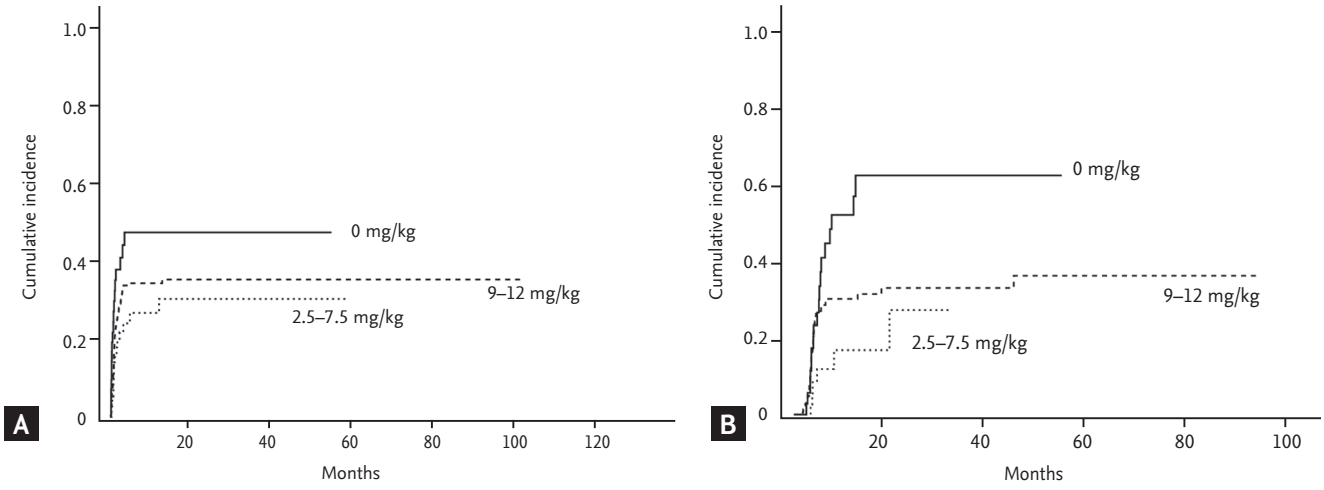

Figure 2. (A) The cumulative incidence rates (CIRs) of grade 2 to 4 acute graft-versus-host disease (GVHD) of the three anti-thymocyte globulin (ATG) groups (0, 2.5 to 7.5, and 9 to 12 mg/kg). (B) The CIRs of extensive chronic GVHD of the three ATG groups.

tively ([HR, 1.519; 95% CI, 1.012 to 2.278; p = 0.044] and [HR, 2.140; 95% CI, 1.299 to 3.524; p = 0.003]). In addition, the CIR of ecGVHD was significantly lower in low to medium ATG group compared to that in no AGT group (HR, 0.447; 95% CI, 0.224 to 0.889; p = 0.022) (Fig. 2B).

DISCUSSION

Our study showed that the low to medium dose of ATG (2.5 to 7.5 mg/kg) was associated with longer survival and lower incidence rates of ecGVHD in patients who underwent HLA mismatched allogeneic HSCT. Moreover, the low to medium dose of ATG did not increase CIR of relapse after HLA mismatched allogeneic HSCT.

The cGVHD occurs in approximately 30% to 70% of patients undergoing allogeneic HSCT of unmanipulated donor grafts and receiving a calcineurin inhibitor and antimetabolite for prophylaxis [14]. All grade aGVHD occurs in 30% to 50% of allogeneic HSCT and grade 3 to 4 GVHD occurs in 14% [15]. There have been many trials which aimed at alleviating aGVHD and cGVHD, improving survival outcomes and reducing relapse [16-18]. The use of ATG has been known to reduce the incidence of GVHD and the severity of cGVHD through in vivo T-cell depletion [19]. However, the optimal dose of ATG with respect to prevent the GVHD is not fully defined.

In the Gruppo Italiano Trapianti Midollo Osseo (GITMO) trial, two studies were conducted on the use of varying ATG doses (no ATG, 7.5 mg/kg of ATG, and 15 mg/kg of ATG) to prevent GVHD due to transplantation from unrelated donors. Use of 15 mg/kg of ATG before HSCT significantly reduced the risk of grade 3 to 4 aGVHD but did not increase the survival owing to the increased risk of infection [20]. In a previous study by Kim et al. [21], low-dose ATG at 2.5 mg/kg showed clinical advantage in prevention of moderate to severe aGVHD in mismatched unrelated HSCT. In addition, low-dose ATG has been reported to improve survival outcomes without the risk of serious infection, and to lower the incidence of aGVHD [22]. In a previous study conducted on mismatched unrelated donor HSCT using 7.5 mg/kg ATG, Pidala et al. [23] reported a lower incidence of severe cGVHD. The CIR of moderate to severe cGVHD was 19% (95% CI, 10 to 36) after 1 year and 28% (95% CI, 16 to 48) after 2 years. OS was 55% (95% CI, 39 to 71) after 1 year and 45% (95% CI, 27 to 63) after 2 years [23]. In a study conducted by the European Group for Blood and Marrow Transplantation (EBMT), patients with AML received allogeneic HSCT from a matched related donor in the CR1 state and were given less than 6 mg/kg of ATG; it was reported that the cGVHD incidence was reduced without an increase in the risk of relapse [24]. Devillier et al. [25] also reported that the ATG dose was a determinant factor associated with relapse and GVHD. However, the dose of ATG used according to the type of transplant and patient were not

determined and individual approaches were needed [26]. The results of this study suggested that low to medium dose of ATG (2.5 to 7.5 mg/kg) would be adequate for better GVHD prophylaxis and better survival outcomes in mismatched HSCT for acute leukemia and MDS. Our study was a multicenter retrospective study involving a relatively large number of patients who underwent mismatched HSCT in eight centers of Korea. Our data would be helpful for selecting the optimal dose of ATG in HLA mismatched HSCT.

However, our study has several limitations. Because our study was a retrospective study, the patient numbers included in each three ATG dose groups were unevenly distributed by physicians discretions and patient population was relatively heterogenous. According to the ATG dose, subsequent infection risk such as by cytomegalovirus and Epstein-Barr virus need to be investigated in further study.

In conclusion, low to medium doses of ATG may be associated with improving survival outcomes and reducing incidence of ecGVHD without increasing the risk of relapse in patients with acute leukemia or MDS undergoing non-TBI-based HLA-mismatched allogeneic HSCT. In the future, we need to investigate precise optimal dose of ATG in HLA-mismatched allogeneic HSCT by performing well-designed prospective clinical studies.

KEY MESSAGE

1. Optimal dose of anti-thymocyte globulin (ATG) is undetermined in human leukocyte antigen mismatched hematopoietic stem cell transplantation.
2. Low to medium dose of ATG (2.5 to 7.5 mg/kg) was associated with longer overall survival and lower incidence rates of extensive chronic graft-versus-host disease.
3. Low to medium dose of ATG did not increase the risk of relapse.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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