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Hematopoietic Stem Cell Transplantation From a Related Donor with Human Leukocyte Antigen 1-Antigen Mismatch in the Graft-Versus-Host Direction Using Low-dose Anti-thymocyte Globulin

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Abstract

Hematopoietic stem cell transplantation (HSCT) from a related donor with an human leukocyte antigen (HLA) 1-antigen mismatch without in vivo T cell depletion is associated with an elevated risk of severe, acute, and chronic graft-versus-host (GVH) disease (GVHD) and poor survival. Therefore, we conducted a multicenter phase II trial of HSCT using low-dose anti-thymocyte globulin (ATG, thymoglobulin). We recruited patients aged 16–65 years with leukemia, myelodysplastic syndrome, or lymphoma who planned to receive HSCT from a related donor with HLA 1-antigen mismatch in the GVH direction at the HLA-A, -B, or -DR locus. Pretransplantation ATG was administered with standard GVHD prophylaxis consisting of tacrolimus and methotrexate. Thirty-eight patients were eligible for the analysis. The 1-year GVHD-free relapse-free survival (GRFS) was 47%. The 3-year overall survival (OS) was 57%. Age of less than 50 years was associated with better OS. OS in patients with high/very high refined disease risk indexes (rDRIs) was comparable to that in those with low/intermediate rDRIs. The 100-day cumulative incidences of grades II–IV and III–IV acute GVHD were 45% and 18%, respectively. HSCT from a related donor with two allele mismatches showed higher incidences of grades II–IV and III–IV acute GVHD. Three-year cumulative incidences of moderate to severe or severe chronic GVHD were 13% and 3%, respectively. HSCT from a related donor with one locus mismatch at the antigen level using low-dose ATG showed lower incidences of acute and chronic GVHD, which led to acceptable GRFS, OS, relapse, and nonrelapse mortality.

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graft-versus-host disease, related donor, HLA 1-locus mismatch, anti-thymocyte globulin

Introduction

An human leukocyte antigen (HLA)–identical sibling is the first choice for donor selection in allogeneic hematopoietic stem cell transplantation (HSCT). For those who do not have an HLA-identical sibling, an HLA-matched unrelated donor (MUD) is an alternative option. However, it is difficult to find an MUD for patients with rare HLA haplotypes. An HLA 1-antigen-related donor has been considered to be one of the best alternative donors[1–4]. Valcarcel et al. reported that transplant outcomes after an HLA 1-antigen mismatched related transplantation were comparable to those after an HLA-MUD transplantation and concluded that HLA 1-antigen mismatched related donors should be the first choice in patients with acute leukemia without an HLA-identical sibling in need of allogeneic HSCT[1]. On the other hand, we previously reported that outcomes after transplantations from a related donor with 1-antigen mismatch at HLA-A, -B, and -DR antigens in the GVH direction are worse than those after HLA-A, -B, -C, and -DRB1-allele matched unrelated transplantations[3]. However, the use of low-dose anti-thymocyte globulin (ATG) was associated with better outcomes by reducing grade III–IV acute graft-versus-host disease (GVHD), extensive chronic GVHD, and nonrelapse mortality (NRM)[4].

Although post-transplant cyclophosphamide (PTCY) after an HLA haploidentical transplantation showed promising clinical outcomes by reducing GVHD and NRM, despite HLA multiple mismatches[5–16], it has not been determined whether ATG or PTCY is superior for HLA 1-locus mismatched related transplantations.

In the present study, we report the result of a multicenter phase II trial of transplantation from a related donor with an HLA 1-antigen mismatch at the HLA-A, HLA-B, or HLA-DR locus in the GVH direction using low-dose ATG as GVHD prophylaxis.

Methods

Study Design

The study was organized by the Japan Society for Hematopoietic Cell Transplantation and approved by the institutional review board of Jichi Medical University Saitama Medical Center (Clinical Trial Registry: UMIN000011192). Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Major inclusion criteria were as follows: (1) patients who are 16–65 years old; (2) patients who have a related donor with an HLA 1-antigen mismatch in the GVH direction; (3) patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), adult T-cell leukemia (ATL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), non-Hodgkin lymphoma (NHL), or Hodgkin lymphoma (HL); (4) patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and (5) patients whose major organ functions (heart, lung, liver, and kidney) are preserved (ejection fraction $\geq$40%, $SaO_2 \geq 94\%$ or $SpO_2 \geq 94\%$ on room air, pulmonary function test: %vital capacity (%VC) $\geq$70%, forced expiratory volume in one second% (FEV1.0%) $\geq$70%, serum total bilirubin $\leq$2.0 mg/dl, and serum aspartate aminotransferase $\leq$5 times the upper normal limit, creatinine clearance $\geq$30 ml/min). Patients with positive donor-specific HLA antibodies were excluded.

GVHD Prophylaxis and Conditioning Regimens

Prophylaxis against GVHD was performed with tacrolimus, methotrexate, and thymoglobulin. Tacrolimus was started on day -1 at a dose of 0.03 mg/kg per day by continuous infusion, and the dose was adjusted to maintain a blood concentration between 12 and 15 ng/ml. Methotrexate was administered at 10 mg/m^2 on day 1 and 7 mg/m^2 on days 3 and 6. For patients with a noninfectious fever on day 11 or before, methotrexate was able to be administered at 7 mg/m^2 on day 11. Thymoglobulin was administered at 1.25 mg/kg per day on days -4 and -3.

The reduced-intensity regimen was selected when the patient's age was 55 years or more, as the myeloablative regimen would not be tolerable due to patient comorbidity. The following conditioning regimens were allowed: myeloablative regimen, total body irradiation (TBI) 12 Gy + cyclophosphamide 120 mg/kg $\pm$ cytarabine 2–12 g/m^2, or busulfan 12.8 mg/kg + cyclophosphamide 120 mg/kg, reduced-intensity regimen with fludarabine 120–180 mg/m^2 + busulfan 6.4–12.8 mg/kg $\pm$ TBI 2–4 Gy, and fludarabine 180 mg/m^2 + melphalan 80–140 mg/m^2 $\pm$ TBI 2–4 Gy.

Endpoints and Definitions

The primary endpoint was 1-year survival without relapse, grade III–IV acute GVHD, or severe chronic GVHD based on NIH criteria (GVHD-free relapse-free survival, GRFS). Other assessed endpoints were overall survival (OS), progression-free survival (PFS), relapse, NRM, neutrophil and platelet engraftment, and acute and chronic GVHD. Neutrophil recovery was defined as an absolute neutrophil count exceeding 500/μl for three consecutive days after transplantation. Platelet recovery was defined as an absolute platelet count exceeding 20,000/μl without a platelet transfusion. Acute GVHD was graded using standard criteria[17], and chronic GVHD was graded using the NIH GVHD criteria[18]. The refined disease risk index (rDRI) was used for the disease risk[19]. Plasma EBV DNA load was monitored

weekly from day 30 until day 100 using real-time polymerase chain reaction methods.

Statistical Analysis

To reject any treatment with a success rate less than 20% with a 5% alpha error and to accept any treatment with a success rate higher than 40% with a 20% beta error, 35 patients were required, but based on the assumption of a 10% loss of patients, we planned a total of 39 patients to be enrolled in this study. The probabilities of GRFS, OS, and PFS were estimated according to the Kaplan–Meier method and the groups were compared using the log-rank test. The probabilities of neutrophil and platelet engraftment, acute and chronic GVHD, and relapse and NRM were estimated on the basis of cumulative incidence curves[20]. Competing events were deaths without an event. The groups were compared using Gray's test[21]. The Cox proportional hazards model was used to evaluate the effect of the variable of interest on GRFS, OS, and PFS, while the competing regression model was used to evaluate its effect on other endpoints[22]. All statistical analyses were performed with Stata version 14 software (Stata Corp., College Station, TX, USA) and EZR (Jichi Medical University Saitama Medical Center, Saitama, Japan)[23].

Results

Patient Characteristics

Thirty-nine patients were registered. One patient was ineligible because their serum aspartate aminotransferase level was more than five times the upper normal limit after registration; therefore, 38 patients were eligible for the analysis. Table 1 shows the patient and transplant characteristics. The median age of the patients included in the study was 51 years (range: 16–64 years). Diagnoses were AML in 14 patients, ALL in 6, MDS in 4, CML in one, NHL in 8, ATL in 4, and HL in 1. In the eight NHL patients, subtypes were peripheral T-cell lymphoma, not otherwise specified in three, NK/T cell lymphoma in three, diffuse large B-cell lymphoma in one, and double-hit lymphoma in one. Eighteen patients received a transplant in CR1 or CP1, 3 in CR2 or more, and 13 in non-CR. One-fourth of the patients had high/very high rDRIs. A total of 26 patients received a myeloablative regimen, and 12 received a reduced-conditioning regimen. Only one patient received additional MTX at day 11 for noninfectious fever. One-third of the patients had two allele mismatches in the GVH direction at the HLA-A, -B, and -DRB1 loci. Most patients (87%) received peripheral blood stem cells. The median follow-up period of the survivors was 2.9 years (range: 1.0–4.4 years).

GVHD-free Relapse-free Survival

The 1-year GRFS was 47% [90% confidence interval (CI), 33%–62%] (Fig. 1A). Since the lower limit of the 90% CI exceeded the predefined threshold of 20%, this protocol was considered to be a success. There was no significant factor that was associated with GRFS in the univariate analysis. However, the 1-year GRFS for patients aged less than 50 years was higher than that for those aged 50 years or more (65% vs 33%, $P = 0.118$) (Fig. 1B). The 1-year GRFS for patients with low/intermediate rDRI and high/very high rDRI or that for those with one allele mismatch and two allele mismatches were comparable (rDRI low/intermediate 50% vs high/very high 40%, $P = 0.980$, one allele mismatch 52% vs two allele mismatches 38%, $P = 0.536$) (Fig. 1C, D).

Neutrophil and Platelet Engraftment

The cumulative incidence of neutrophil engraftment at day 42 was 97% (95% CI, 64%–100%) (Fig. 2A). The cumulative incidence of platelet engraftment at day 100 was 82% (95% CI, 64%–91%) (Fig. 2B). There was no primary or secondary graft failure.

Acute and Chronic GVHD

The cumulative incidences of grades II–IV and III–IV acute GVHD at day 100 were 45% (95% CI, 28%–60%) and 18% (95% CI, 8%–32%), respectively (Fig. 3A, B).

Lymphocyte counts just before ATG administration were categorized into two groups (high lymphocyte and low lymphocyte) according to the median value of 311/μl. There was no significant difference in grade II–IV or III–IV between these two groups, although the incidence of grade III–IV acute GVHD was higher in the high lymphocyte group (Fig. 3C, D). The incidence of grade II–IV acute GVHD in the group with two allele mismatches at HLA-A, -B, and -DRB1 was higher than that in the group with one allele mismatch, although there was no statistical difference (Fig. 3E, F). Even if HLA-C is considered in HLA matching, there was no statistical difference (Fig. 3G, H). Grade III–IV acute GVHD was observed in 8 of 33 patients receiving peripheral blood stem cell transplantation, but none in 8 patients receiving bone marrow transplantation. Acute GVHD was treated with a median dose of 1 mg/kg of methylprednisolone or prednisolone for 15 patients and an overall treatment response was obtained in 12 patients.

The cumulative incidence of any grade, moderate to severe, and severe chronic GVHD at 3 years was 29% (95% CI, 15%–44%), 13% (95% CI, 5%–26%), and 3% (95% CI, 2%–12%), respectively (Fig. 4). There was no significant factor associated with chronic GVHD in the univariate analysis.

For patients who survived without relapse, the rate of discontinuation of immunosuppressants at 1 year was 75% (95% CI, 54%–86%) (Fig. 5).

Overall and Progression-free Survival

The 3-year OS was 57% (95% CI, 39%–71%) (Fig. 6A). Age less than 50 years was associated with better OS (80% vs

Table 1.

Variable		$n = 38$	
Recipient age, median (range)		51 (16–64)	
Recipient sex	Female	15	39.5%
	Male	23	60.5%
Disease	ALL	6	15.8%
	AML	14	36.8%
	ATL	4	10.5%
	CML	1	2.6%
	HL	1	2.6%
	MDS	4	10.5%
	NHL	8	21.1%
Disease risk	CR1/CP1	18	47.4%
	CR2-	3	7.9%
	Non-CR	13	34.2%
	Other status	4	10.5%
Refined disease risk index	Low/intermediate	28	73.7%
	High/very high	10	26.3%
Days from diagnosis to transplant, median (range)		188 (108–7,007)	
History of prior autologous transplantation	Yes	2	5.3%
	No	36	94.7%
HCT-CI	0	25	65.8%
	1	7	18.4%
	2	2	5.3%
	3	4	10.5%
Conditioning regimen	Myeloablative	26	68.4%
	Reduced intensity	12	31.6%
GVHD prophylaxis	Tac + MTX d1, 3, 6	37	97.4%
	Tac + MTX d1, 3, 6, 11	1	2.6%
Use of G-CSF	Yes	33	86.8%
	No	5	13.2%
Sex match between recipient and donor	Match	15	39.5%
	Male to female	10	26.3%
	Female to male	13	34.2%
Relationship of donor	Brother	8	21.1%
	Sister	10	26.3%
	Father	2	5.3%
	Mother	3	7.9%
	Son	10	26.3%
	Daughter	5	13.2%
CMV antibody	Either positive	37	97.4%
	Both negative	1	2.6%
Source	Bone marrow	5	13.2%
	Peripheral blood	33	86.8%
Antigen mismatch in GVH at HLA-A, -B, -DR	1	38	100.0%
Antigen mismatch in HVG at HLA-A, -B, -DR	0	1	2.6%
	1	27	71.1%
	2	9	23.7%
	3	1	2.6%
Allele mismatch in GVH at HLA-A, -B, -DRB1	1	25	65.8%
	2	13	34.2%
Allele mismatch in HVG at HLA-A, -B, -DRB1	0	1	2.6%
	1	19	50.0%
	2	14	36.8%
	3	4	10.5%
Antigen mismatch in GVH at HLA-A, -B, -C, -DR	1	23	60.5%
	2	11	28.9%
	Missing	4	10.5%

(continued)

Table 1. (continued)

Variable		$n = 38$	
Antigen mismatch in HVG at HLA-A, -B, -C, -DR	0	1	2.6%
	1	14	36.8%
	2	14	36.8%
	3	4	10.5%
	4	1	2.6%
	Missing	4	10.5%
Allele mismatch in GVH at HLA-A, -B, -C, -DRB1	1	16	42.1%
	2	12	31.6%
	3	6	15.8%
	Missing	4	10.5%
Allele mismatch in HVG at HLA-A, -B, -C, -DRB1	0	1	2.6%
	1	10	26.3%
	2	12	31.6%
	3	10	26.3%
	4	1	2.6%
	Missing	4	10.5%
Follow-up of survivors (years), median (range)		2.9 (1.0–4.4)	

ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; ATL: adult T-cell leukemia; CML: chronic myelogenous leukemia; CMV: cytomegalovirus; CP: chronic phase; CR: complete remission; G-CSF: granulocyte-colony stimulating factor; GVH: graft-versus-host; GVHD: graft-versus-host disease; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; HL: Hodgkin lymphoma; HVG: host-versus-graft; MDS: myelodysplastic syndrome; MTX: methotrexate; NHL: non-Hodgkin lymphoma; Tac: tacrolimus.

38%, $P = 0.004$) (Fig. 6B). OS in patients with high/very high rDRIs was comparable to OS in those with low/intermediate rDRIs (70% vs 53%, $P = 0.318$) (Fig. 6C). The 3-year PFS was 57% (95% CI, 39%–71%) (Fig. 6D). Age less than 50 years was associated with better OS (80% vs 38%, $P = 0.004$) (Fig. 6E). PFS in patients with high/very high rDRIs was comparable to PFS in those with low/intermediate rDRIs (70% vs 53%, $P = 0.318$) (Fig. 6F).

Relapse and NRM

The cumulative incidence of relapse and NRM at 3 years was 28% (95% CI, 14%–43%) and 24% (95% CI, 12%–38%), respectively (Fig. 7). There were no significant variables associated with the incidence of relapse, including rDRIs (low/intermediate rDRI 26% vs high/very high rDRI 30%, $P = 0.706$). For NRM, age was the only significant variable in the univariate analysis. The cumulative incidence of NRM at 3 years in patients aged 50 years or older was significantly higher than that in those less than 50 years old (43% vs 0%, $P = 0.002$). Causes of patient death in the NRM group ($n = 9$) were GVHD in one, infection in one, organ failure in two, thrombotic microangiopathy in two, acute respiratory distress syndrome in two, and interstitial pneumonia in one.

Transplant Complications

CMV disease developed in four (colitis: three and gastritis: one). Median onset of CMV disease after transplantation was 36 (range: 27–54). Two of them developed after the treatment of acute GVHD. All of them recovered after ganciclovir or foscarnet treatment. Two patients had HHV-6 encephalitis at days 20 and 27 after transplantation, and both of them recovered after foscarnet treatment. EBV reactivation of >1,000 copies/μl in peripheral blood occurred in four patients [median onset; 37 (range: 30–44)]. None received preemptive therapy of rituximab for post-transplant lymphoproliferative disorder (PTLD) or developed PTLD. The EBV level increased along with NHL disease progression in one patient. Seven patients had hemorrhagic cystitis (BK virus: four, BK virus + JC virus: one, adenovirus: one, and unknown: one). Median onset of hemorrhagic cystitis after transplantation was 50 (range: 14–221). HSV infection was observed in one patient at day 221 after transplantation. Two patients developed hepatic veno-occlusive disease and six developed thrombotic microangiopathy.

Discussion

In this phase II trial, we showed that transplantation from a related donor with one locus mismatch at the antigen level using low-dose ATG showed relatively low incidences of acute and chronic GVHD. These effects led to acceptable GRFS, OS, relapse, and NRM. However, a high incidence of grade II–IV acute GVHD in the two allele mismatched group suggested that a higher ATG dose may be required.

Several studies have shown that the administration of ATG decreased the incidence of chronic GVHD and improved quality of life and GRFS[4,24–30]. In a phase III trial of ATG (total of 4.5 mg/kg thymoglobulin) versus no ATG for unrelated transplantation, more patients successfully discontinued immunosuppressants, and GRFS was significantly better in the ATG group than in the non-ATG group[24]. On the contrary, in another phase III trial of ATG (total of 20 mg/kg of Grafalon) versus no ATG for unrelated transplantation, there was no significant difference in GRFS between

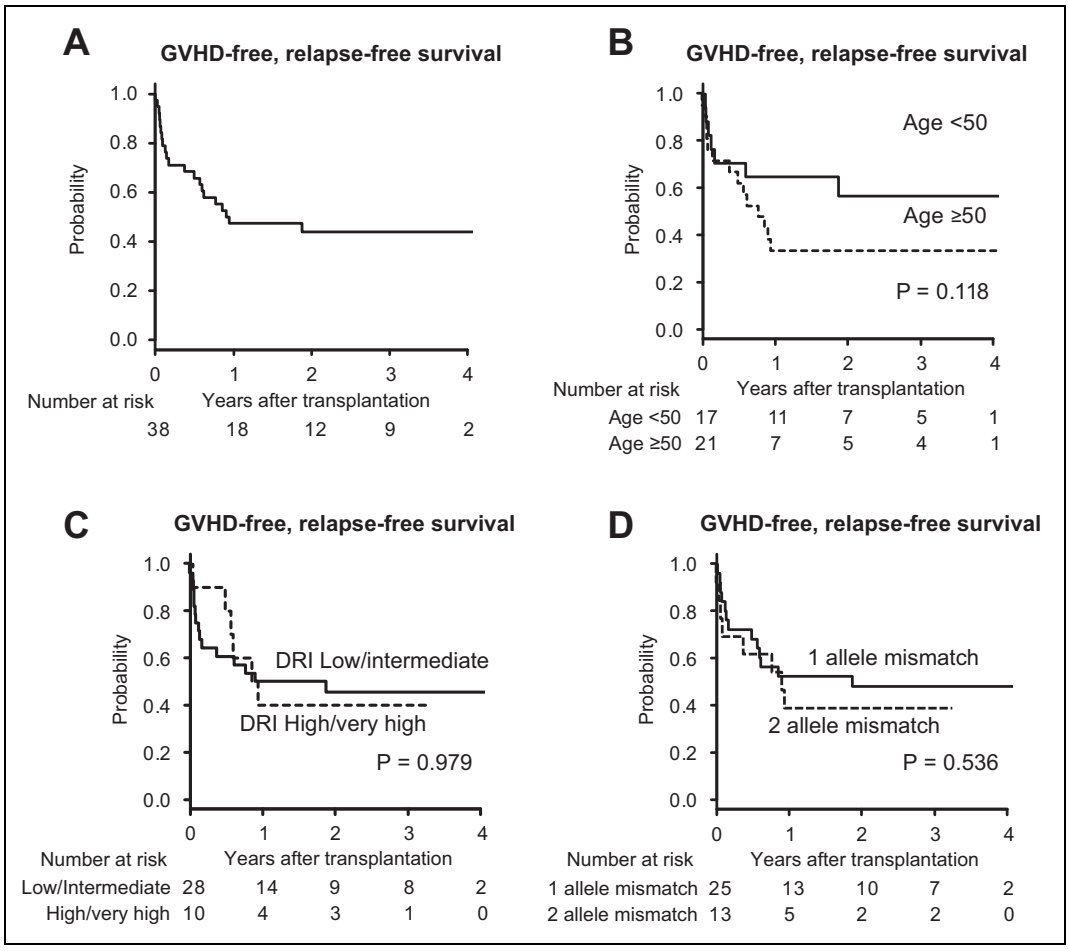

Fig. 1. GVHD-free, relapse-free survival for the total cohorts (A), and those stratified by age group (B), disease risk index (C), and the number of allele mismatches at the HLA-A, -B, or -DRB1 locus (D). GVHD: graft-versus-host disease.

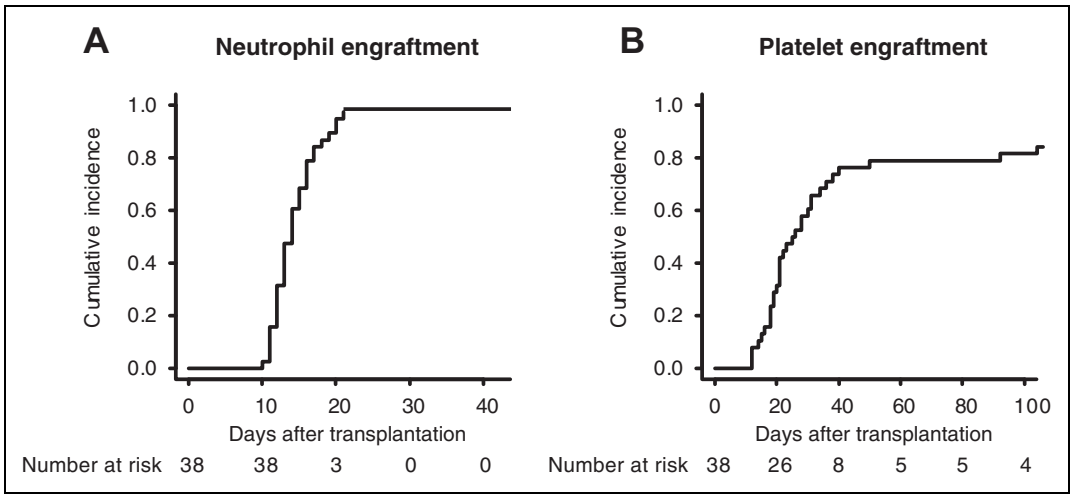

Fig. 2. Neutrophil (A) and platelet engraftment (B) for the total cohorts.

the two groups, and OS in the ATG group was lower than that in the non-ATG group, although the incidences of grade II–IV acute GVHD and moderate to severe chronic GVHD were lower in the ATG group[25]. This discrepancy between the two phase III trials may be partly due to the difference in the ATG itself or in the dose of ATG. High doses of ATG may not only reduce chronic GVHD but also increase the risk of infection and NRM. In retrospective studies, low-dose

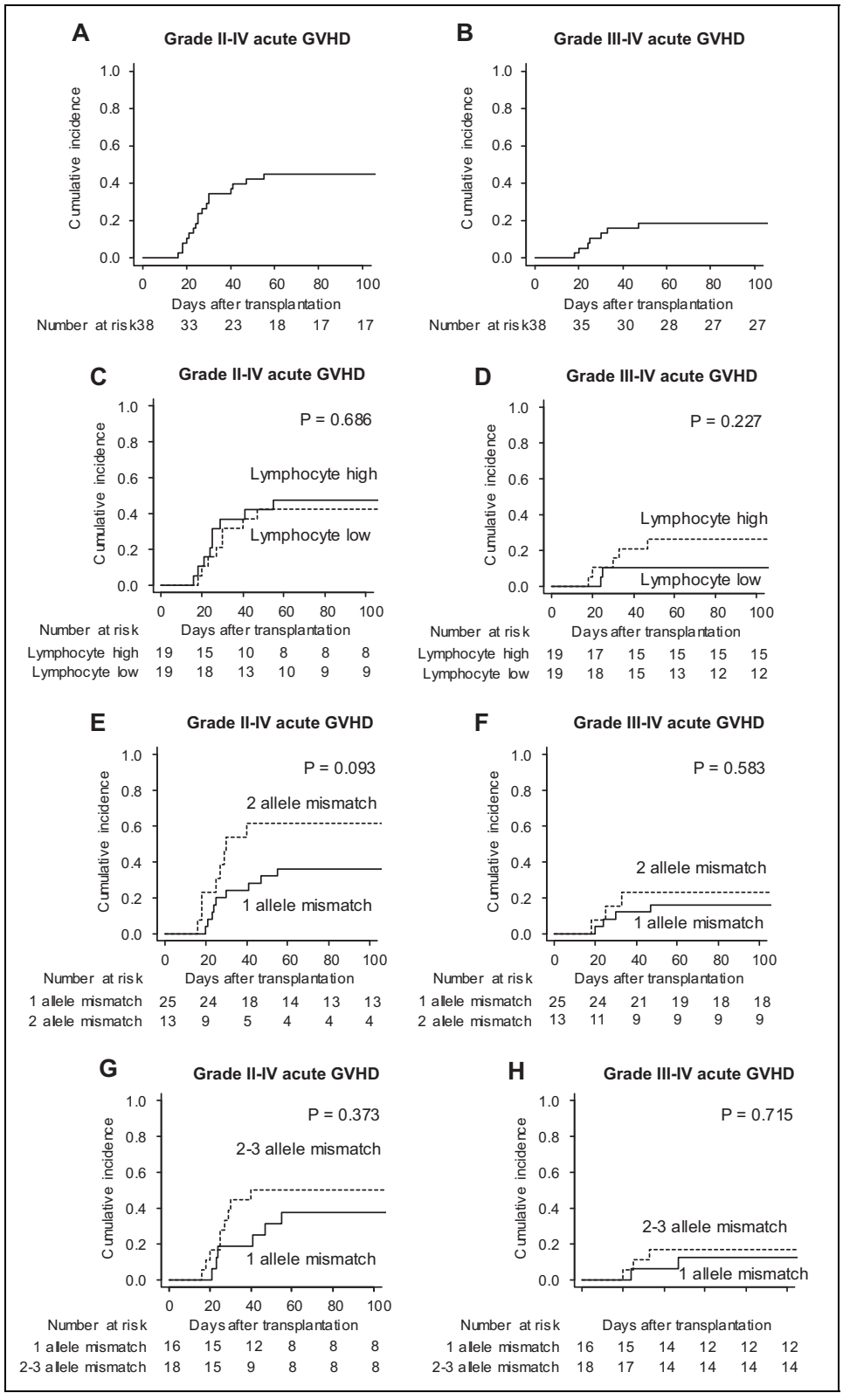

Fig. 3. Grades II–IV and III–IV acute GVHD for the total cohorts (A, B), and those stratified by lymphocyte counts (C, D), and the number of allele mismatches at the HLA-A, -B, or DRB1 locus (E, F) and at the HLA-A, -B, -C, or -DRB1 locus (G, H). GVHD: graft-versus-host disease.

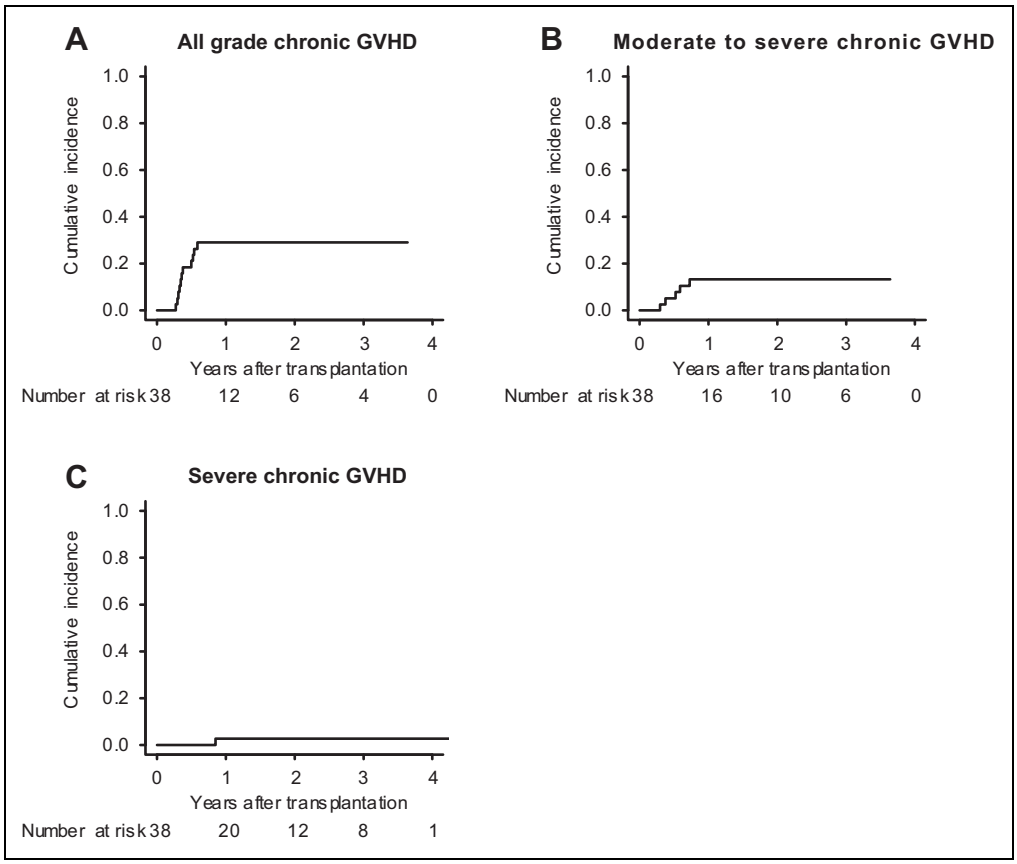

Fig. 4. Chronic GVHD of all grades (A), moderate to severe (B), and severe chronic GVHD (C) for the total cohorts. GVHD: graft-versus-host disease.

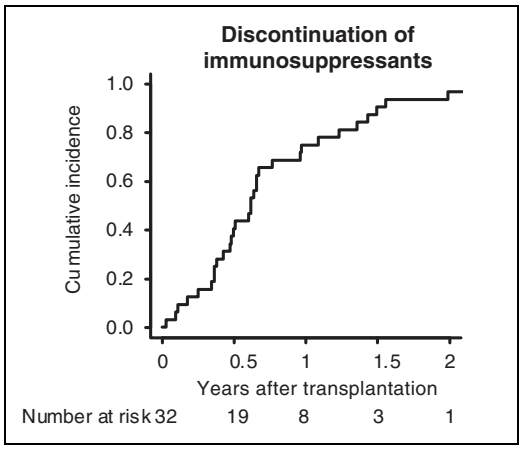

Fig. 5. Rate of discontinuation of immunosuppressants among those who survived without relapse.

ATG has been shown to decrease the risk of GVHD and improve GRFS[4,28,30]. In our prospective study, we observed a low incidence of chronic GVHD and acceptable GRFS, OS, relapse, and NRM.

However, the incidences of grades II–IV and III–IV acute GVHD at 100 days were 45% and 18%, respectively, which were higher than those observed in our previous retrospective study[4]. The incidence of grade III–IV acute GVHD was about 10% for patients receiving transplantation from one locus mismatched donors with T-cell depletion in that study. A possible reason for this discrepancy is the frequent use of peripheral blood stem cells (PBSC) in this cohort (87%) in this prospective study, as compared with our previous retrospective study (52%), since the use of PBSC could be the risk of acute GVHD. Second is the HLA counting methods. Since the cohort recruited transplantation from related donors with one antigen mismatch at the HLA-A, -B, or -DR locus, the group included two allele mismatches. The higher incidence of acute GVHD may be due in part to the two allele mismatches in this group. The incidence of acute GVHD was higher in the two allele mismatched group than in the one allele mismatched group, although this difference was not statistically significant. A thymoglobulin dose of 2.5 mg/kg may not be sufficient for multiple allele mismatches among the one antigen mismatched group. Whether the HLA-C locus should also be considered is another issue to be investigated in the future.

Recently Admiraal et al. reported that the lymphocyte count just prior to ATG administration was associated with the risk of GVHD, and this was confirmed in another

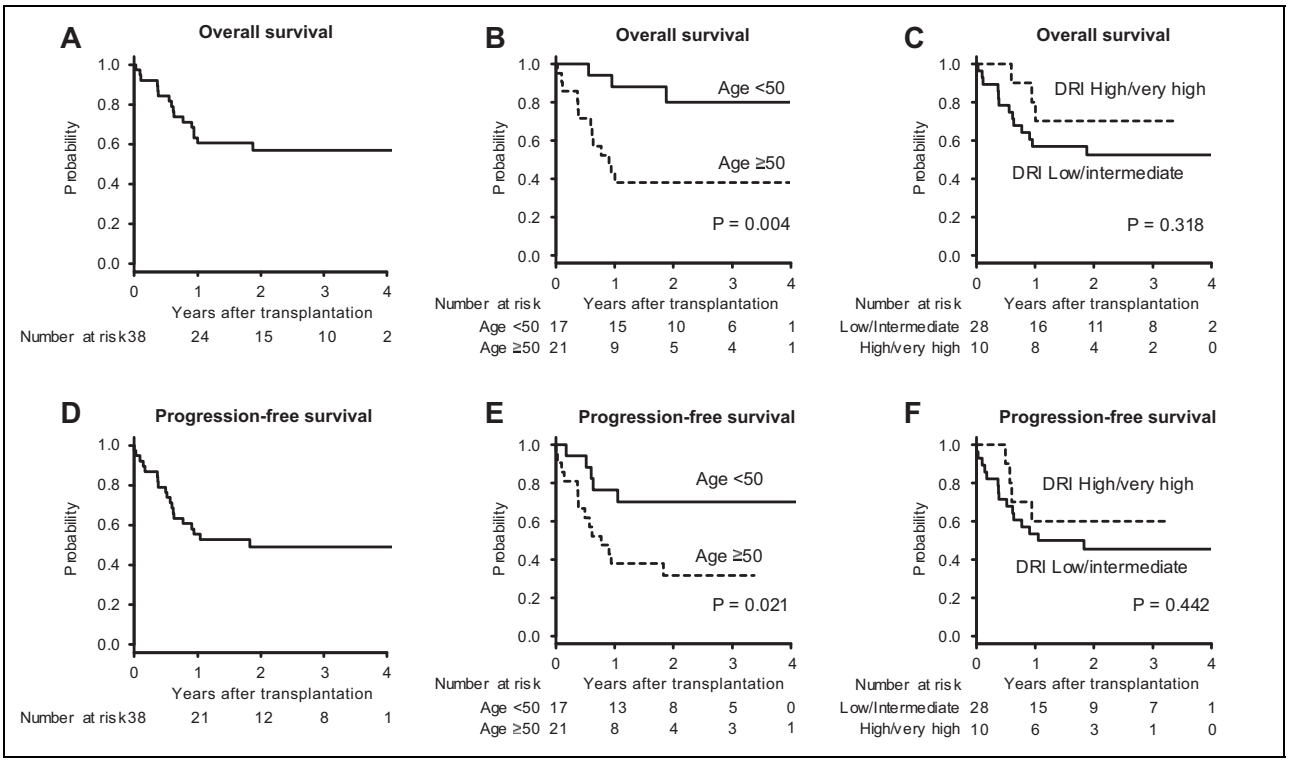

Fig. 6. Overall and progression-free survival for the total cohorts (A, D), and those stratified by age group (B, E) and disease risk index (C, F).

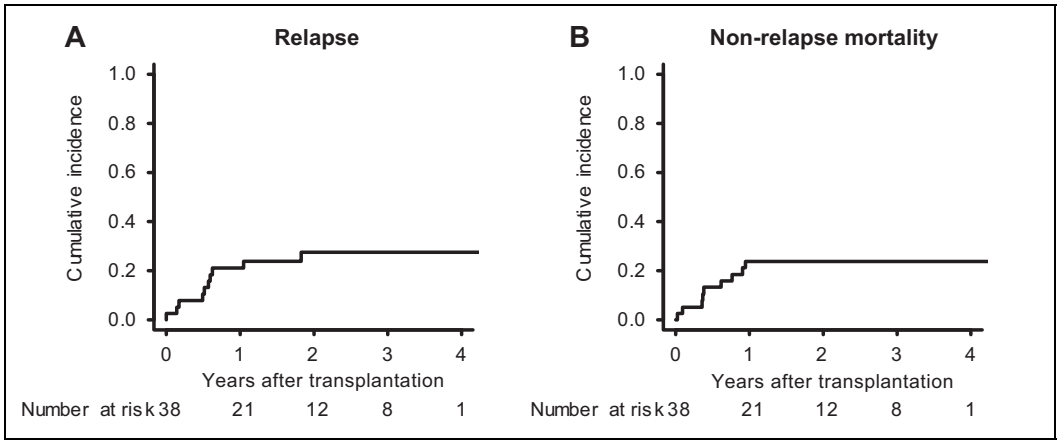

Fig. 7. Relapse (A) and nonrelapse mortality (B) for the total cohorts.

study[25,31]. In the present study, we divided the cohort into two groups according to the median value of the lymphocyte count. Although this difference was not statistically significant, the incidence of grade III–IV acute GVHD was higher in the high lymphocyte group. The dose of ATG may need to be adjusted according to the number of allele mismatches and the number of lymphocytes prior to ATG administration. These should be tested in a future prospective study.

In haploidentical transplantation, PTCY after HLA haploidentical transplantation showed promising clinical outcomes by reducing GVHD and NRM, regardless of the number of HLA multiple mismatches[5–16]. PTCY is superior to ATG in terms of leukemia-free survival and GRFS, lower GVHD, and lower NRM, regardless of the sources and conditioning intensity[32]. However, in the case of transplantation from a related donor with an HLA 1-antigen mismatch, there is no clear solution. The impact of ATG on relapse is an important issue. The relapse incidence was comparable between the low/intermediate and high/very high rDRI groups. Further, we previously showed that the use of ATG

was not associated with the risk of relapse in transplantation from a related donor with an HLA 1-antigen mismatch. These findings suggested the presence of GVL effects, even in patients with a high risk of relapse in transplantation from a related donor with an HLA 1-antigen mismatch using low-dose ATG. On the other hand, the high incidence of grade III–IV acute GVHD, particularly in the two allele mismatch group, suggests the need for an increase in the dose of ATG or the use of PTCY instead of ATG. Although a related donor with an HLA 1-antigen mismatch can be found in 30% of Japanese families, such transplantation is relatively rare and it is difficult to perform a randomized study comparing PTCY and ATG.

In conclusion, HSCT from a related donor with one locus mismatch at the antigen level using low-dose ATG showed lower incidences of acute and chronic GVHD compared to the use of previous strategies without in vivo T cell depletion. These effects led to acceptable GRFS, OS, relapse, and NRM. However, higher incidences of grade II–IV acute GVHD were observed with two allele mismatches. A higher ATG dose may be required for HSCT from a related donor with two or more allele mismatches. Considering the rarity of this kind of transplantation, a matched pair analysis of ATG versus non-ATG in HSCT from a related donor with one locus mismatch at the antigen level may warrant consideration.

Acknowledgments

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Authors Contribution

JK and YK designed the protocol, organized the project, and wrote the manuscript; JK performed the statistical analysis and analyzed the data; TA, SIK, SIF, KI, SF, and TT recruited patients; YA contributed to the data collection; and all of the authors interpreted the data and reviewed and approved the final manuscript.

Ethical Approval

The study was approved by the institutional review board of Jichi Medical University Saitama Medical Center (Clinical Trial Registry: UMIN000011192).

Statement of Human and animal Rights

All procedures in this study were conducted in accordance with the Jichi Medical University Saitama Medical Center approved protocols (Clinical Trial Registry: UMIN000011192).

Statement of Informed Consent

Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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