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PROGRESS IN HEMATOLOGY

Recent progress in allogeneic stem cell transplantation using alternative stem cell sources

Effect of antithymocyte globulin on HLA-mismatched unrelated transplantation

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Abstract

HLA 1-locus-mismatched unrelated donors (1MMUD) are often considered as alternative donors in allogeneic hematopoietic stem-cell transplantation (allo-HCT) when an HLA-matched related or unrelated donor is unavailable. However, HLA mismatch remains a major risk factor for acute and chronic graft-versus-host disease (GVHD). Antithymocyte globulin (ATG) has been used to prevent acute and chronic GVHD, and multiple studies have shown that use of ATG is associated with decreased acute and chronic GVHD, which is associated with improved QOL. However, at high doses, ATG may lead to an increase in fatal infection, relapse, or delayed engraftment. The optimal ATG dose for MMUD remains unclear. The optimal ATG dose should be determined based on a fine balance between the reduction of GVHD and the risk of relapse, fatal infection, and/or delayed engraftment. Interestingly, promising results from some recent Asian studies suggest that a low dose of ATG may improve non-relapse mortality and overall survival without increasing relapse or fatal infection in allo-HCT from an HLA-mismatched unrelated donor. A randomized control trial is expected to confirm these results in Japan. In addition, pharmacokinetic/pharmacodynamic studies may help to identify the personalized optimal ATG dose.

Keywords Allogeneic hematopoietic transplantation · HLA-mismatched unrelated donor · Antithymocyte globulin · Graft-versus-host disease · Optimal ATG dose

Introduction

An HLA-matched unrelated donor (MUD) is considered to be the best alternative donor in allogeneic hematopoietic stem-cell transplantation (allo-HCT) for patients who lack an HLA-matched related donor (MRD), because the transplant outcomes from MUD are comparable to those from MRD [1–3]. However, at least 70% of patients in Japan do not have a MRD, and it is difficult to find a MUD for patients who have rare HLA haplotypes. Therefore, as shown in Fig. 1, it is not uncommon for alternative donor sources to be selected in allo-HCT. In addition to an HLA 1-locus-mismatched-related donor, umbilical cord blood and HLA-haploidentical donor, an HLA 1-locus-mismatched unrelated donor (1MMUD) has been considered to be an alternative donor in allo-HCT when an HLA-matched related or unrelated donor is unavailable. On the other hand, it is not yet clear which donor source is most suitable as a third donor selection. Therefore, the third donor is selected according to the experience of each institution and/or the patient disease status and clinical condition.

In general, when an unrelated donor is selected, HLA-A, HLA-B, HLA-C, and HLA-DRB1 (± HLA-DQB1) alleles are genotyped in each patient and donor prior to allo-HCT. HLA-mismatching remains a major risk factor for acute and chronic graft-versus-host disease (GVHD) in unrelated transplantation. As a result, overall survival (OS) in allo-HCT from an HLA-mismatched unrelated donor (MMUD) has been shown to be inferior to that of allo-HCT from MUD [4–8]. While antithymocyte or antilymphocyte globulin (ATG) has been used for the prevention of acute and chronic GVHD, ATG can also lead to delayed immune reconstitution of T cells, resulting in increased relapse or infection [9]. Several randomized control trials have evaluated the efficacy

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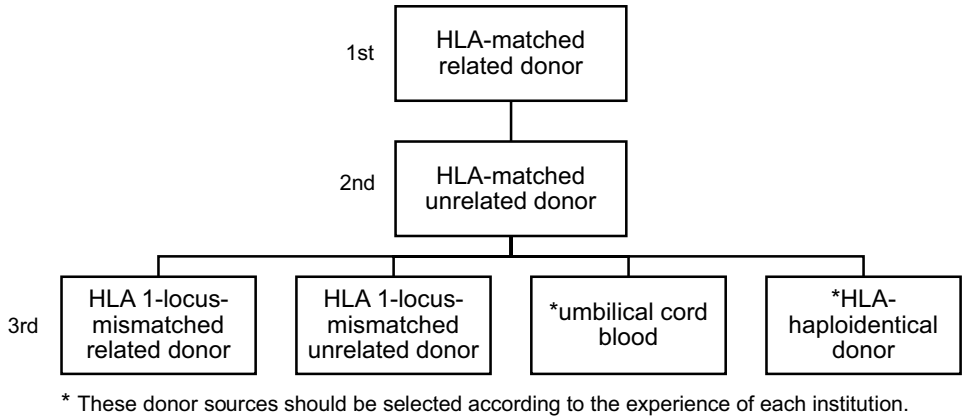

Fig. 1 Algorithm used for the donor search in allogeneic hematopoietic stem cell transplantation. *These donor sources should be selected according to the experience of each institution

of ATG in allo-HCT (Table 1) [10–17]. The incidence of acute and chronic GVHD was significantly lower in the ATG group, but there were no significant differences in relapse rate, non-relapse mortality, or overall survival between the two groups, except for one study. However, the efficacy of ATG for MMUD remains unclear, because most patients in these trials received allo-HCT from MUD or MRD. Therefore, this review focuses on the role of ATG in adult patients who receive allo-HCT from MMUD.

ATG formulation and mechanisms

ATG is a polyclonal immunoglobulin preparation obtained by immunizing animals with human thymocytes (thymoglobulin [Sanofi, Paris, France] and ATGAM [Pfizer, New York, NY]) or Jurkat T lymphoblastoid cells (ATG-Fresenius (ATG-F) [Neovii Biotech, Graefelfing, Germany]) [18]. Thymoglobulin and ATG-F are produced by immunized rabbit, and ATGAM is produced by immunized horse. Lymphoglobulin (Genzyme, Cambridge, MA), which was produced by horse immunized with human thymocytes, was withdrawn from the market in the late 2000s. ATGAM is unavailable in many countries, except for the USA. In Japan, thymoglobulin is the only ATG formulation approved for GVHD prophylaxis under the Japanese National Health Insurance system. Therefore, this review covers rabbit ATG, especially thymoglobulin.

ATG consists of polyclonal antibodies against multiple antigens expressed on T cells, B cells, natural killer cells, dendritic cells, and so on. Thus, ATG has the following diverse effects on the immune system: T-cell depletion in blood and peripheral lymphoid tissues through complement-dependent lysis and T-cell activation and apoptosis, induction of B-cell apoptosis, modulation of key cell-surface molecules that mediate leukocyte/endothelium interactions, interference with the functional properties of dendritic cells, and induction of Treg and NK-T cells [18, 19]. Therefore, ATG is used for GVHD prophylaxis and treatment [20], treatment of severe aplastic anemia [21, 22], and prevention or rescue treatment of acute rejection in organ transplantation [23].

Transplant outcomes by ATG as GVHD prophylaxis

Limited data are available for evaluating the efficacy of ATG as GVHD prophylaxis in allo-HCT from MMUD. Table 2 summarizes the results of retrospective studies on ATG in unrelated allo-HCT. However, there are insufficient data on MMUD. Therefore, this review evaluated the impact of ATG on allo-HCT from MMUD with reference to the results of MUD and a related donor.

GVHD

The use of ATG reduced the incidences of acute and/or chronic GVHD in all of the randomized control trials and most of the retrospective studies (Tables 1, 2). This was confirmed by a meta-analysis of the randomized control trials [24–27]. In general, the risk of acute and chronic GVHD is higher in allo-HCT from MMUD than in that from MUD [4–8]. Thus, the use of ATG for GVHD prophylaxis is reasonable in allo-HCT from MMUD. In addition, reduction of GVHD, especially chronic GVHD, is expected to improve quality of life (QOL) after allo-HCT, since chronic GVHD is associated with impaired QOL [28–31]. Two randomized control trials suggested that ATG could improve QOL [11, 15]. Moreover, multiple studies have also reported that the probability of immunosuppressive treatment-free survival was higher in patients who received ATG [13, 15, 32, 33].

Table 1 Results of randomized control trials on ATG in allo-HCT

	Dose (mg/kg)	Control	Donor	Graft source	Engraft-ment*	Acute GVHD	Chronic GVHD	Relapse	NRM	OS
Bacigalupo et al. [10, 11]	7.5 (T)	Non-ATG	MUD	BM	→	→	↓[c]	↑	↑	↑
	15 (T)	Non-ATG	MUD	BM	→[a]	↓	↓[c]	↑	↑	↑
Finke et al. [12–14]	60 (F)	Non-ATG	MUD	PBSC/BM	←	↓	↓	↑	↑	↑
Walker et al. [15]	4.5 (T)	Non-ATG	MUD/1MMUD	PBSC/BM	→[b]	↓	↓	↑	↑	↑
Kröger et al. [16]	30 (F)	Non-ATG	MRD	PBSC	←	↓	↓	↑	↑	↑
Soiffer et al. [17]	60 (F)	Non-ATG	MUD	PBSC/BM	←	↓	↓	↑	↑	→

*An upward pointing arrow means delayed neutrophil and/or platelet engraftment in the ATG group

ATG antithymocyte/antilymphocyte globulin, *T* thymoglobulin, *F* ATG-Fresenius, *MUD* HLA-matched unrelated donor, *MMUD* HLA-mismatched unrelated donor, *MRD* HLA-matched related donor, *BM* bone marrow, *PB* peripheral blood stem cell, *GVHD* graft-versus-host disease, *NRM* non-relapse mortality, *OS* overall survival

[a]Delayed platelet engraftment was noted in the ATG group

[b]Neutrophil engraftment tended to be longer in the ATG group than in the non-ATG group (median 17.0 days versus 15.0 days, HR 0.70 95% CI 0.52–1.20, $p = 0.277$)

[c]The results reflect the combination of two studies (7.5 (T) and 15 (T))

Engraftment

In 3 of 6 randomized trials, the median times to neutrophil and platelet engraftment in the ATG group were longer by 3–7 days and 7–17 days than those in the non-ATG group [12, 16, 17]. No significant difference was found in the other trials, although delayed platelet engraftment was noted in the 15 mg/kg group, but not the 7.5 mg/kg group, in the GITMO study [10, 15]. These 3 trials used ATG-F (total dose 30–60 mg/kg), while the other 3 trials used thymoglobulin (total dose 4.5–15 mg/kg). A meta-analysis of the randomized trials demonstrated that neutrophil engraftment was significantly delayed (median 2.66 days) [26]. On the other hand, ATG had no impact on neutrophil or platelet engraftment in retrospective studies that targeted unrelated donors (Table 2). This discrepancy may be due to the difference in the method of ATG preparation and/or the ATG dose, and the presence of HLA-mismatching in addition to the retrospective nature of the study. Further studies are necessary to assess the influence of ATG on neutrophil and platelet engraftment in the MMUD setting.

Infection

Some studies have reported that a higher dose of ATG is associated with a higher incidence of infection [10, 34–36]. Bacigalupo et al. reported that a higher dose of thymoglobulin (15 mg/kg) increased the risk of fatal infection, whereas thymoglobulin at 7.5 mg/kg did not [10]. Remberger et al. also showed that thymoglobulin at 10 mg/kg tended to increase infectious mortality in comparison with thymoglobulin at 4–8 mg/kg [34]. These results suggested that a high dose of ATG could cause fatal infection.

A major concern is whether the use of ATG leads to an increase in viral reactivation such as of cytomegalovirus (CMV) or Epstein-Barr virus (EBV). The use of ATG is considered to be a risk factor for EBV-post-transplantation lymphoproliferative disorders (PTLDs) [37]. Walker et al. reported that EBV reactivation was more common in a ATG group than in a non-ATG group [15]. A meta-analysis showed increased incidences of CMV and EBV reactivation (risk ratio 1.25 and 1.33) [26]. Although a low dose of ATG may not increase fatal infections, it is unclear whether it increases viral infections such as by CMV or EBV. Therefore, viral reactivation should be monitored carefully when ATG is used.

Non-relapse mortality

No significant differences in non-relapse mortality were found between the ATG group and the non-ATG group in randomized control trials, although the incidences of GVHD significantly differed (Table 1). While the precise reason for

Table 2 Results of retrospective studies on ATG in allo-HCT from an unrelated donor

	Dose (mg/kg)	Control	Donor	Graft source	Engraft-ment	Acute GVHD	Chronic GVHD	Relapse	NRM/TRM	OS
Zander et al. [38]	≥40 (F)	Non-ATG	MUD/MMUD	BM/PBSC	↓	↓	↓	→	↓	↑
Shattenberg et al. [45]	8–16 (T)	Non-ATG	MUD	BM	Not given[c]	↓	→	→	↓	↑
Remberger et al. [34]	6–10 (T)	4 (T)	MUD	BM/PBSC	→	↓	→	→	→*	→*
Basara et al. [54]	5–15 (T) 45–60 (F)	Non-ATG	MUD/1MMUD	BM/PBSC	→	→	↓	→	→	→
Kim et al. [39]	2.5 (T)	Non-ATG	1-2MMUD	BM/PBSC	→	↓	→	→	↓	↑
Mohty et al. [55]	Various (T)	Non-ATG	MUD	BM/PBSC	→	→	↓	→	→	→
Remberger et al. [43]	8 (T)	6 (T)	MUD	BM/PBSC	→	→	→	↑	→	→
Fuji et al. [32]	5–10 (F)	Non-ATG[b]	MUD/MMUD	BM	→	↓	↓	→	↓	→
Kuriyama et al. [33]	1–4 (T)	Non-ATG	MUD/MMUD	BM/PBSC	→	→	↓	→	→	→
Kawamura et al. [40]	Various (T)[a]	Non-ATG	1MMUD	BM	→	↓	→	→	↓	↑

*The median dose of thymoglobulin (6–8 mg/kg) was associated with lower TRM and better OS

ATG antithymocyte globulin, *T* thymoglobulin, *F* ATG-Fresenius, *MUD* HLA-matched unrelated donor, *MMUD* HLA-mismatched unrelated donors, *MRD* HLA-matched related donor, *BM* bone marrow, *PB* peripheral blood stem cell, *GVHD* graft-versus-host disease, *NRM* non-relapse mortality, *TRM* transplant-related mortality, *OS* overall survival

[a]Median 2.5 mg/kg (range 1.0–11.0 mg/kg)

[b]Reduced-intensity conditioning regimen with low-dose TBI (2 or 4 Gy)

[c]The incidence of rejection was significantly higher in the non-ATG group

this finding is not clear, the incidence of infection might influence this result. On the other hand, some retrospective studies that included MMUD showed that the use of ATG was associated with lower non-relapse mortality [32, 34, 38–40]. We reported that non-relapse mortality in the ATG group was lower than that in the non-ATG group (HR 0.35; 95% CI 0.19–0.65; $p < 0.001$) in patients who received allo-HCT from 1MMUD using a recent Japanese registry data [40]. This may suggest that the advantage of ATG (reduction of GVHD) outweighs the disadvantage (risk of infection) in allo-HCT from MMUD.

Relapse

As shown in Tables 1 and 2, there was no significant difference in relapse rate between the ATG group and the non-ATG group in randomized control trials and retrospective studies. On the other hand, two large retrospective studies reported that reduced-intensity conditioning (RIC) with ATG was associated with a higher relapse rate [41, 42]. However, the dose of ATG was unclear and several donor types (MRD, MUD, and/or MMUD) were included in these two studies. Interestingly, Remberger et al. showed that a higher dose of thymoglobulin (8 mg/kg) increased the incidence of relapse in comparison with an intermediate dose (6 mg/kg) after RIC allo-HCT from MUD [43]. The European Group for Blood and Marrow Transplantation (EBMT) study also reported that a higher dose of thymoglobulin (≥ 6 mg/kg) significantly increased the risk of relapse for acute myeloid leukemia patients who received RIC allo-HCT from an HLA-matched sibling [44]. On the other hand, Korean and Japanese studies showed that low-dose ATG was not associated with a high risk of relapse in the setting of MMUD [32, 33, 39, 40]. Therefore, a low or intermediate dose of ATG may not increase the risk of relapse in allo-HCT from MMUD, although we should still pay attention in the RIC setting because of limited data.

Overall survival

In 5 of 6 randomized control trials, ATG was not associated with an improvement of OS (Table 1) [10–16]. On the other hand, Soiffer et al. reported that OS was lower in the ATG group [17]. Although the cause of this difference is not clear, the dose of ATG and/or donor type might have influenced the results. As shown in Table 2, some retrospective studies showed that OS in the ATG group was superior to that in the non-ATG group in allo-HCT from an unrelated donor, especially MMUD [38–40, 45]. A Japanese retrospective study showed that the use of low-dose thymoglobulin (median 2.5 mg/kg) significantly decreased not only acute GVHD, but also non-relapse mortality, without increasing relapse, resulting in an improvement of OS in allo-HCT from 1MMUD [40]. Kim et al. reported comparable results in allo-HCT from MMUD in Korea [39]. These results suggest that the use of ATG may improve OS in patients who received allo-HCT from MMUD, at least in Asia. The use of ATG for MMUD may be more effective than that for MUD or MRD because HLA-mismatch is a risk factor for GVHD.

Optimal ATG dose and timing

The optimal ATG dose in allo-HCT from MMUD remains unclear. Although a high ATG dose could reduce the incidence of acute and chronic GVHD, it may lead to an increase in fatal infection, relapse, or delayed engraftment due to delayed immune reconstitution of T cells. On the other hand, a low ATG dose may decrease infection and/or relapse, but may be insufficient to prevent GVHD. Thus, we should determine the optimal ATG dose based on a delicate balance between the reduction of GVHD and the risk of relapse, fatal infection, and/or delayed engraftment. This balance may vary according to the risk of GVHD and the disease condition, such as donor type, stem cell source, race, conditioning regimen, and disease stage. The EBMT and the European LeukemiaNet working group recommend that the dose of ATG-F should be 30 mg/kg and that of thymoglobulin should be 7.5 mg/kg in allo-HCT from MUD [20]. On the other hand, Japanese and Korean studies showed that a low dose of thymoglobulin (median 2.5 mg/kg) could lead to promising transplant outcomes despite allo-HCT from 1 to 2 MMUD [39, 40]. These results suggest that the optimal ATG dose for Asian patients may be lower than that for Caucasian patients. The difference may be due to the risk of GVHD, because several studies have demonstrated that the incidence of GVHD in Asian patients is lower than that in Caucasian patients [46–48]. In addition, peripheral blood stem cells have been commonly used in unrelated transplantation in the Europe and the United states [49, 50], whereas bone marrow has been still widely used in Japan. Some studies have shown that the risk of GVHD is higher in allo-HCT of peripheral blood stem cells from an unrelated donor than in that of bone marrow [51, 52]. Therefore, the difference of the dominant stem-cell source may affect the ATG dose. Thus, the optimal ATG dose may be differ according to stem cell sources. Japanese patients may receive great benefit from, ATG because only low-dose ATG can control GVHD and lead to decreases in fatal infection and relapse, resulting in the improvement of OS. Interestingly, a randomized controlled trial is being conducted to evaluate the efficacy of low-dose ATG (thymoglobulin: 2.5 mg/kg) for patients in Japan who received allo-HCT from 1MMUD (UMIN000028008). This trial is expected to evaluate the efficacy of low-dose ATG for 1MMUD and determine the optimal dose of ATG for Japanese patients.

Pharmacokinetic/Pharmacodynamic (PK/PD) studies are also important for evaluating the optimal dose of ATG. Admiraal et al. recently reported that an optimum ATG exposure was associated with higher overall survival because of lower relapse-related mortality and lower non-relapse mortality, whereas a below-optimum ATG exposure increased GVHD and non-relapse mortality, and an above-optimum ATG exposure increased relapse [53]. Interestingly, they showed that recipient's absolute lymphocyte count before administration of ATG was the relevant predictor for ATG pharmacokinetics in adults. Thus, the optimum ATG dose may have to be determined based on absolute lymphocyte count rather than bodyweight. In addition, the timing of ATG administration may also affect transplant outcomes. The late administration of ATG may lead to a decrease in GVHD, but delayed engraftment, in comparison with the early administration of ATG [9]. However, there are insufficient data to determine the optimal timing of ATG administration. The optimal timing probably interacts with the ATG dose. Therefore, it is necessary to investigate the timing of ATG in conjunction with the ATG dose.

Conclusions and future perspectives

The use of ATG in allo-HCT from MMUD can be a promising intervention approach for not only preventing acute and chronic GVHD but also improving QOL. In addition, ATG may improve OS through lower non-relapse mortality, if a low or intermediate dose of ATG can control GVHD despite a higher risk of GVHD for MMUD. Further studies are necessary to evaluate the effect of ATG in various settings, because the optimal dose and timing of ATG for MMUD remain unclear. PK/PD studies may also help to identify the personalized optimal ATG dose. Furthermore, careful monitoring, and prophylaxis and pretreatment of viral reactivation may further improve overall survival by reducing viral infections such as by CMV or EBV. Therefore, 1MMUD is expected to be a suitable alternative donor if the optimal dose of ATG is used.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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