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The role of anti-thymocyte globulin in preventing graft rejection and acute graft-versus-host disease after allogenic hematopoietic stem cell transplantation

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Summary

Acute GVHD and graft rejection are the main early complications of allo-SCT. In our research, we analyzed the probability of development of early complications in 109 patients with different oncohematological diseases. We evaluated the results of 112 allo-SCTs from related and unrelated donors subjected to myeloablative and nonmyeloablative conditioning regimens, either with or without ATG. The usage of ATG provides effective control over aGVHD, without increasing the risk of a relapse of the basic disease, and reduces the probability of graft rejection to 7%. Consequently, our data on ATG application in allo-HSCT demonstrates its ability to effectively decrease the risk of early complications post-transplant, thus favoring an increase of 4-year overall survival, in comparison to the control group, where ATG was not used.

Keywords: anti-thymocyte globulin, hematopoietic stem cell transplantation, Graft-versus-host disease, graft rejection

Introduction

The broad application of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is still limited by the immunological recognition and destruction of host tissues, termed graft-versus-host disease (GVHD). The role of inflammatory cytokines and their impact on immune effectors (mainly CD4+ and CD8+ T cells) has been extensively studied in the context of the GVHD occurring after standard myeloablative allo-SCT. Reduced-intensity conditioning (RIC) regimens are being increasingly used with allo-SCT. RIC has been shown to allow engraftment with minimal early transplantation-related mortality (TRM). However, in the context of RIC, predictive factors for acute and chronic graft-versus-host disease (aGVHD and cGVHD, respectively) and their effect on the outcome remain unknown. Moreover, the graft versus leukemia reaction (GVLR) was closely associated with GVHD.

However, recent data suggests that GVHD pathophysiology is likely to involve more complex interactions, where antigen-presenting cells, especially dendritic cells (DCs), may play a major role at the time of initiation of acute GVHD [9-10, 13].

The success of allogeneic stem cell transplantation owes much to improvements in the immunosuppressive regimens that prevent GVHD and reduce graft rejection risk. Previous studies have shown that the removal of T-cells from the graft via ex vivo T-cell depletion resulted in a dramatic decrease in aGVHD. This has been shown to be associated with a significant increase in graft failure and the risk of relapse, even in studies in which T-cell add-back has been investigated. An alternative strategy is to provide for in vivo T-cell depletion by using anti-thymocyte globulin (ATG) as a part of the conditioning regimen.

The common belief is that ATG‘s efficacy relies on its capacity to deplete T-lymphocytes, but the polyclonal nature of ATG is reflected in its diverse effects on the immune system: (1) T-cell depletion of blood and peripheral lymphoid tissues through complement-dependent lysis and T-cell activation and apoptosis; (2) modulation of key cell surface molecules that mediate leukocyte/endothelium interactions; (3) induction of apoptosis in B-cell lineages; (4) interference with dendritic cell functional properties; and (5) induction of regulatory T-cells and natural killer T-cells [9-13]. As a consequence, ATG provides a multifaceted immunomodulation, thus paving the way for future applications and suggesting that the use of ATG should be included in the immunosuppressive therapeutic armamentarium, thereby helping to reduce the incidence of graft rejection and GVHD.

Until now there has been no satisfactory evidence of these ATG benefits in such patients, because the decrease of graft rejection probability and GVHD severity could have been connected with an increasing relapse rate [2, 5]. Thus, in our study we have evaluated the application of ATG within conditioning regimens for increasing effectiveness of HSCT.

Materials and methods

There were 109 patients enrolled, who underwent 112 hematopoietic stem cell transplantations (HSCT) from related and unrelated donors at the Bone Marrow Transplantation Department

at Saint-Petersburg Pavlov State Medical University from October 2000 until June 2006.

Patients were divided into two groups to test the use of ATG in conditioning regimens: (1) the experimental group, where ATG was used at a dosage of 16–120 mg/kg per cycle; this group enrolled 74 patients with 74 allo-SCT, and (2) the control group, where ATG was not used in conditioning regimens; it included 35 patients with 38 allo-SCT. Patient characteristics are listed in Table 1.

Table 1. Patient characteristics in groups with vs. without ATG treatment

Clinical features	ATG-treated (n=74)	ATG not applied (n=38)
Median age, years (range)	15 (1–66)	18 (5–56)
Diagnosis (%)		
ALL	34 (48)	18 (47)
AML	14 (20)	9 (24)
CML	9 (12)	5 (13)
NHL	4 (5)	2 (5)
HD	1 (1)	2 (5)
AA	7 (9)	0 (0)
MDS	1 (1)	0 (0)
Hypereosinophilic syndrome	0 (0)	1 (3)
Solid tumors	0 (0)	1 (3)
Kostman syndrome	1 (1)	0 (0)
Krabbe disease	1 (1)	0 (0)
Wiscott-Aldrich syndrome	1 (1)	0 (0)
Idiopathic osteomyelofibrosis	1 (1)	0 (0)
Remission (%)		
CR1/CP1	9 (12.2)	7 (18.4)
Advanced disease	65 (87.8)	31 (81.6)
Graft source (%)		
Bone marrow	23 (31)	19 (50)
Peripheral blood	51 (69)	19 (50)
Conditioning regimens (%)		
Reduced intensity (RIC)	43 (58)	15 (39)
Myeloablative conditioning	31 (42)	23 (61)
Donor (%)		
related	12 (16)	31 (82)
unrelated	62 (84)	7 (18)

Table 2. Outcomes of allo-HCT with *vs.* without ATG treatment

	with ATG (n= 74), %	**without ATG (n= 38), %**	**P**
Graft failure	7	24	**.01**
Grades II-IV GVHD	38	41	.5
Grades III-IV GVHD	14	24	.2
Relapse, 4 y	29	47	.07
- RIC regimens, 3 y	35	67	**.03**
- myeloablative regimens, 4 y	27	36	.6
Survival, 4 y	39	28	.1

Combinations of immunosuppressive drugs were employed, in accordance with international HSCT protocols, for GVHD prophylaxis in the post-transplant period. CsA was administered at 3–5 mg/kg, starting on Day 1 before HSCT, until Day 150–180 post-transplant depending on biochemical parameters and CsA concentrations in the blood plasma.

The main criteria of engraftment were the recovery of neutrophil levels to >0.5 x10^9/L during 3 consequent days without using CSF, an increase in platelet counts to >20x10^9/L, and an elevation of blood hemoglobin to>80 g/L without blood transfusions.

Results and discussion

According to many studies, the probability of graft rejection post-HSCT varies from 1% to 5%. In patients with aplastic anemia with multiple transfusions in their history, this event may be as high as 43% [3]. Adding ATG to the conditioning regimens in such patients could decrease graft rejection rates up to 9% [6].

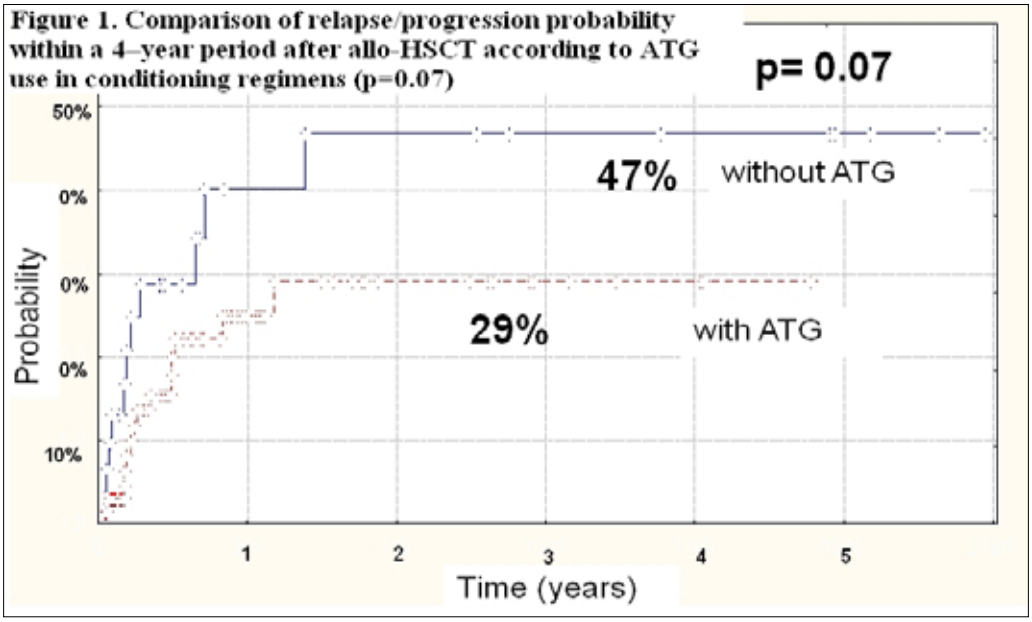
In our study we have shown that an intensification of graft rejection prophylaxis with ATG helps to reduce the rate of such complications. In the experimental group, primary graft rejection was revealed in 3 patients (4%). Two patients (3%) developed late graft rejection after Day +100. The use of ATG in their conditioning regimens showed a positive correlation with decreased graft rejection rate, when compared with the control group: 7% vs. 24% (p=0.01), respectively (Table 2).

The results also show a significant reduction of graft rejection risk in association with ATG use in unrelated allo-HSCT (p=0.02). In patients treated with ATG in unrelated allo-SCT, the graft rejection rate was 5%, whereas the probability of such complications in the control group was 6 times higher, presenting in 29% of cases. However, ATG effectiveness for prevention of graft rejection in related allo-HSCTs is less obvious (p> 0.05).

A relatively high incidence of transplant rejection in our study, as compared with other data from literature, may be connected with

some clinical features of most patients, who were continuously pretreated before HSCT, or transplanted during incomplete clinical remissions. A group of standard-risk patients (CR1/CP1) did not exceed 19% of the allo-HSCT group under study (Table 1).

Acute GVHD is one of the main complications after allo-SCT and occurs in 30% of cases. In allo-HCT from unrelated HLA-matched donors, the probability of aGVHD increases to 80% [1]. Clinical signs of aGVHD are considered to reflect only a part of recipient immunological response to donor cell injection. Another component of immune response in HSCT is presented by GVL (graft-versus-leukemia) reaction, which develops in parallel with aGVHD. Thereby, aGVHD is a biological marker of the anti-relapse effects of donor cells in allo-HSCT. Lymphocytes, recovered from bone marrow, could identify antigenic determinants expressed on leukemic cells, and eliminate them quite effectively. However, despite the complete HLA-compatibility of donor and recipient, donor-derived immune cells could also detect minor histocompatibility antigens (MHA) on the host cells, and induce an acute graft-versus-host reaction. Meanwhile, the usage of ATG in conditioning regimens for preventing such complications helps to decrease the aGVHD risk to 14%, comparing with 24% in control (Table 2).



According to the literature, severe aGVHD develops more often in patients with unrelated allo-SCT compared with transplantations from related donors. In many cases it is associated with mismatches for minor histocompatibility antigens. We have shown, however, that among patients without ATG, occurrence of severe aGVHD (grade III–IV) was similar for cases of related versus unrelated transplants. There were no cases of severe aGVHD when using ATG in related allo-SCT, whereas in patients without ATG, aGVHD of grade III–IV occurred in 20.8% of cases. Additionally, a two-fold decrease in severe aGVHD rates among ATG-treated patients, as compared with the control group, was shown after unrelated allo-SCT, i.e., 16.6% vs. 40%, respectively. However, due to low numbers of patients with related HSCT in the ATG group, and unrelated HSCT in the control group, these results are not statistically significant ($p > 0.05$).

In recent years, it has been realized that absolute myeloablation is not an obligate condition for engraftment, and the immunoadaptive cytostatic action of donor cells in most cases may exceed the cytostatic effects of radio and chemotherapy [2, 4, 5, 7, 8]. These observations justified an increasing popularity of reduced toxicity regimens in clinical practice, because of their low toxic effects on bone marrow and other organs, and higher tolerability in aged patients with concomitant diseases.

Comparing the rates of relapse and/or progression within a period of 4 years after HCT in the main and control groups, we have not observed any increase in such complications among patients with ATG (29%) vs. patients without ATG (47%) (Fig.1).

According to our data, the application of reduced toxicity regimens with ATG contributes to a significantly lower risk of relapse/ progression within a period of 3 years when compared with the control group: 35% and 67%, respectively (p= 0.03), whereas such a difference was not so evident among the patients after myeloablative conditioning regimens: 27% vs. 36% (p= 0.6).

Overall four-year survival in patients with ATG was 39%, while in the control group it was under 28% (Fig.2).

In summary, ATG use in the experimental group provided a decrease in the death rate in the early post-transplant period, due to a reduction of graft rejection rates and milder aGVHD severity, as compared with patients from the control group who didn't receive ATG.

Conclusions

1. Administration of anti-thymocyte globulin (ATG) contributes to an increased four-year overall survival rate of 39%, as compared with 28% among the patients of the control group who did not receive ATG.
2. Addition of ATG to conditioning regimens reduces the probability of graft rejection.
3. ATG administration is associated with decreased rates of severe aGVHD (grade III–IV).
4. ATG application does not lead to increased relapse rates.

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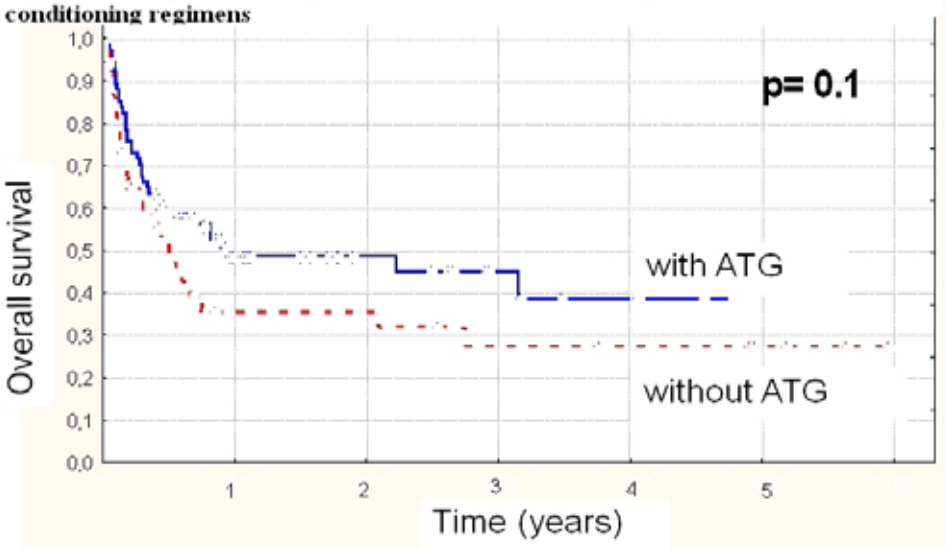
Figure 2. Comparison of 4-year overall survival according to ATG use in conditioning regimens



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Роль антитимоцитарного глобулина в профилактике отторжения трансплантата и острой болезни «трансплантат против хозяина» (РТПХ) после аллогенной трансплантации гемопоэтических стволовых клеток (алло-ТГСК)

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Резюме

Основными ранними осложнениями алло-ТГСК являются острая РТПХ и реакция отторжения трансплантата. В нашем исследовании проанализирована возможность развития этих ранних осложнений у 109 больных с различными онкогематологическими заболеваниями. Проведены 112 алло-ТГСК от родственных и неродственных доноров при миелоаблативных или немиелоаблативных режимах кондиционирования с введением антитимоцитарного глобулина (АТГ) или без него. Применение АТГ обеспечивает эффективный контроль при РТПХ без повышения риска рецидива основного заболевания и снижает вероятность отторжения трансплантата до 7%. В целом, использование АТГ, по нашим данным, связано с эффективным снижением риска ранних посттрансплантационных осложнений. Введение АТГ приводит к повышению средней 4-летней выживаемости больных до 39% по сравнению с 28% в контрольной группе Применение АТГ ассоциировано со снижением частоты развития тяжелых форм РТПХ (III-IV степени). Кроме того, использование АТГ не сопровождается возрастанием частоты рецидивов. Таким образом, применение АТГ у трансплантационных больных обеспечивает снижение гибели больных в раннем посттрансплантационном периоде в связи со снижением риска отторжения трансплантата и тяжести РТПХ по сравнению с контрольной группой, в которой больные не получали АТГ.

Ключевые слова: антитимоцитарный глобулин, трансплантация гемопоэтических стволовых клеток, реакция «трансплантат против хозяина», отторжение трансплантата