Chapter 3

Antithymocyteglobulin as prophylaxis of graft failure and graft-versus-host disease in recipients of partially T cell depleted grafts from matched unrelated donors: a dose finding study

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Abstract

In this study, we set out to evaluate the effect of 3 different Antithymocyteglobulin (ATG) doses on graft failure and incidence of graft-versus-host disease (GVHD) among recipients of partially T cell depleted (TCD) grafts from matched unrelated donors (MUDs). Data of 74 consecutively treated MUD recipients were analysed. Fifty-two, 13 and 9 MUD patients were treated with ATG in a total dose of 8 mg/kg, 6 mg/kg and 4 mg/kg (given from days -8 until -4), respectively. Granulocyte and platelet engraftment was not different between the groups, while graft failure was observed in two patients only (receiving 8 mg/kg and 4 mg/kg ATG, respectively). The cumulative incidence of severe (grade III-IV) acute GVHD and extensive chronic GVHD was 4%, 0%, 44% and 11%, 8%, 44% in groups receiving ATG in a dose of 8 mg/kg, 6 mg/kg and 4 mg/kg, respectively (severe acute GVHD: $p < 0.001$; extensive chronic GVHD: $p = 0.05$). Based on these findings, we recommend when ATG is used in the setting of stem cell transplantation with (partially) TCD grafts from MUDs, to give a total dose of 6-8 mg/kg. A further decrease in dosage resulted in a highly significant increased incidence of severe acute and extensive chronic GVHD.

Introduction

Despite improvements in HLA typing, graft-versus-host disease (GVHD) is still a major cause of morbidity and mortality after stem cell transplantation (SCT) with grafts from matched unrelated donors (MUDs). T cell depletion (TCD) of grafts is an effective method for prevention of GVHD[1-4]. However, one of the limitations associated with this method is the occurrence of graft failure[3,4]. A large International Bone Marrow Transplant Registry (IBMTR) analysis learned that the risk for graft failure was related to the type of TCD, being lowest when T cell specific techniques were used[3]. Varying strategies are used to prevent graft failure, which is considered to be mediated by residual host T cells having survived the conditioning regimen[5,6]. A method commonly used in the setting of SCT with TCD grafts from MUDs, is the in vivo pre-transplant depletion of host immune cells using Antithymocyte-globulin (ATG) or Campath-1[4]. Several studies also showed effectiveness of in vivo TCD, using ATG or Campath-1, as prophylaxis of GVHD after MUD transplantation[7-18]. The optimal dose of ATG with respect to prevention of graft failure and severe GVHD is not known. The immunosuppressive and direct toxic effects of ATG, however, necessitate the use of the lowest possible dose.

Here, we set out to evaluate the effect of 3 different ATG (Thymoglobulin™, Sangstat) doses on graft failure and incidence of acute and chronic GVHD among MUD recipients of partially TCD grafts.

Methods

Patients For this study data of 74 patients receiving stem cells from MUDs were analysed. Transplantations were performed between January 1999 and May 2002 at the Department of Haematology of the University Medical Centre Utrecht and at the Department of Haematology of the Erasmus Medical Centre Rotterdam, the Netherlands. ATG (Thymoglobulin™, Sangstat, Amstelveen, the Netherlands) was given pre-transplant to prevent graft failure. Because of the immunosuppressive and direct toxic effects of ATG it was decided in November 2001 to decrease the total dose of ATG from 8 to 6 mg/kg in the Utrecht centre and from 8 to 4 mg/kg in the Rotterdam centre. Thirty-three and 19 MUD

recipients were treated with ATG in a total dose of 8 mg/kg, given in 4 days, and were defined as MUD group 1 (treated in Utrecht) and 2 (treated in Rotterdam), respectively. Thirteen and 9 patients received ATG in a total dose of 6 mg/kg and 4 mg/kg (also given in 4 days), respectively, and were defined as MUD group 3 (treated in Utrecht) and 4 (treated in Rotterdam), respectively. Patients with acute leukaemia in first complete remission, chronic myeloid leukaemia in first chronic phase and untreated severe aplastic anaemia were considered low-risk. All patients with other diseases were considered high-risk. Patients were treated according to clinical protocols approved by the local investigation review boards after informed consent was obtained.

Transplantation procedure The transplantation procedure in both centres was identical. The conditioning regimen consisted of cyclophosphamide (60 mg/kg/day for 2 days), followed by total body irradiation (600 cGy/day for 2 days) with partial shielding of the lungs (total lung dose 850 cGy). The graft was infused after the second TBI fraction (day 0). ATG was given in 4 days, from day -8 until day -4, before cyclophosphamide was infused. Post-transplant immunosuppression consisted of cyclosporin which was discontinued within 3 months after transplantation, when no active GVHD was present. Infection prevention for all patients consisted of ciprofloxacin, fluconazole and amphotericin B given orally until granulocyte counts exceeded 500 cells/μl. Cephalothin was given intravenously for 10 days from day +3. Furthermore co-trimoxazole and (val)acyclovir were given orally from day +1 until 12 months post-BMT or longer in case of active GVHD, in a dose of 480 mg b.i.d. and 500 mg b.i.d., respectively. GVHD was classified according to the Seattle criteria[19] and graft failure according to criteria described by Kernan et al and McGlave et al[1,2].

CMV monitoring Until April 2001 CMV monitoring was performed three times a week using a pp65 assay as described[20]. Since then monitoring was performed once a week using a real-time Taqman™ CMV DNA PCR. However, in patients with active GVHD and in patients with a CMV reactivation, monitoring was performed twice a week. CMV reactivation was defined as CMV pp65 antigenemia of $\geq$ 1 positive staining granulocyte/150.000 cells or CMV DNA viral load (VL) of > 1000 copies/ml.

CMV disease Patients with symptoms of pneumonia, gastritis or enteritis underwent bronchoscopy, gastroscopy or sigmoidoscopy, respectively. CMV pneumonia/gastritis/enteritis was defined histologically by typical cytopathic effects and immunohistochemically by immunofluorescence with use of monoclonal antibodies to immediate early CMV antigens in biopsy specimens. When cultures of BAL fluid, saliva, urine and buffy coat were performed

in case of infectious complications, these included always CMV cultures, irrespective of CMV serostatus.

Ganciclovir therapy CMV-seropositive patients who demonstrated CMV reactivation or who were treated with high-dose corticosteroids for acute GVHD grade II-IV received pre-emptive or prophylactic therapy, respectively, with ganciclovir in a dose of 2.5 mg/kg intravenously twice a day for 14 days. When patients were symptomatic (unexplained fever or symptoms compatible with CMV disease), CMV antigenemia/VL was rising or remained positive after 14 days of treatment, ganciclovir dose was doubled or foscarnet treatment was started instead of ganciclovir in a dose of 60 mg/kg twice a day for 14 days. CMV disease was treated with ganciclovir 5 mg/kg twice a day for at least 14 days and continued until symptoms resolved and antigenemia/VL became negative. In case of disease progression or rising antigenemia/VL foscarnet treatment was started instead of ganciclovir in a dose of 60 mg/kg twice a day. Furthermore, treatment with CMV specific immunoglobulins was added to antiviral therapy in patients with CMV pneumonia.

HLA-matching Class I antigens were analysed by serological and low resolution molecular typing with sequence specific primers (SSP). Since July 2000, high resolution molecular typing (with SSP and/or sequence based typing (SBT)) of HLA-A and B antigens was performed as well. Analyses of class II antigens were performed by high resolution molecular typing with SSP and/or SBT throughout the whole study period. The aim was to obtain a fully matched (for HLA-A, B, Cw, DRB1 and DQB1) or, if not available, an one HLA antigen mismatched unrelated patient/donor pair.

BMT In vitro TCD of bone marrow (BM) was performed using the Sheep Red Blood Cell technique (Rotterdam) or the immunorosette depletion technique (Utrecht) as described[20]. Only 3 patients received a peripheral blood stem cell (PBSC) graft (one from group 1, one from group 2 and one from group 3). TCD of these G-CSF stimulated PBSC grafts was performed by positive selection of CD34+ cells (CliniMacs™, Miltenyi Biotec, Bergisch Gladbach, Germany). After these maximal TCD procedures the residual number of T cells was counted and nonmanipulated T cells (from a small BM/PBSC fraction that was set apart) were added to obtain the desired fixed low number of T cells (1-2 x 10^5 T cells/kg recipient weight).

Statistical analysis Differences between groups were compared using Pearson chi-square analyses in case of discrete variables. In case of continuous variables univariate analysis of variance (ANOVA) or Kruskal-Wallis test, whichever was appropriate, was per-

formed. Overall survival (OS) was estimated by the Kaplan-Meier method. Probabilities of transplant related mortality (TRM), relapse related mortality (RRM), acute GVHD and chronic GVHD were calculated by the cumulative incidence procedure; death without TRM, RRM, acute GVHD and chronic GVHD, respectively, being the competing risk. Univariate analyses were performed using the log rank test. Calculations were performed using SPSS/PC+ 10.0 (SPSS Inc, Chicago Il, USA).

Results

Pre-transplant patient characteristics (Table 1). The percentage of HLA antigen mismatched grafts and mean T cell and CD34+ cell counts of grafts were higher in recipients from MUD group 3 (treated with ATG 6 mg/kg) compared with the other groups,

Table 1 Patient characteristics

	MUD group 1 (n=33)	MUD group 2 (n=19)	MUD group 3 (n=13)	MUD group 4 (n=9)	P
ATG dose	8 mg/kg	8 mg/kg	6 mg/kg	4 mg/kg	
Age, yr	34	34	35	37	ns
(range)	(17-55)	(18-48)	(18-53)	(19-51)	
Diagnosis, %					
AML	18	26	46	13	
ALL	30	11	15	13	
CML	30	21	23	37	
SAA	0	0	0	13	
Other	21	42	15	25	
CMV serostatus R/D, %					ns
+/+	24	16	15	0	
+/-	15	26	54	38	
-/+	15	11	8	25	
-/-	46	47	23	38	
R/D sex, %					ns
M/F	21	16	8	13	
Others	79	84	92	87	
Risk status, %					ns
Low	18	26	15	0	
High	82	74	85	100	
Mean CD3+ cells[&]	2.2	1.6	2.4	1.9	0.008
(range)	(2-4)	(1-4)	(2-5)	(1-3)	
Mean CD34+ cells[&&]	1.62	1.50	2.76	1.66	0.052
(range)	(0.5-5.9)	(0.55-3.24)	(0.95-10.4)	(0.81-2.96)	
Mismatched graft, %	18	11	46	25	ns

R/D = recipient/donor; [&] = in graft, x10^5/kg; [&&] = in graft, x10^6/kg.

although this was only significant for mean T and CD34+ cell counts of grafts (p=0.008 and p=0.052, respectively).

Effect of ATG dose on engraftment and GVHD (Tables 2 and 3, Figure 1). Granulocyte and platelet engraftment was not different between the four MUD groups (Table 2). Graft failure was observed in two patients, who were excluded from analyses, one

Table 2 Platelet and granulocyte engraftment

	MUD group 1 (n=33)	MUD group 2 (n=19)	MUD group 3 (n=13)	MUD group 4 (n=9)	P
ATG dose	8 mg/kg	8 mg/kg	6 mg/kg	4 mg/kg	
Platelets > 50 × 10^9/L					
Recovery, %	94	84	100	78	ns
Median days,	26	32	20	41	ns
(range)	(12-208)	(15-112)	(11-52)	(20-158)	
Granulocytes > 500 × 10^6/L					
Recovery, %	100	100	100	100	ns
Median days,	19	23	19	20	ns
(range)	(12-92)	(11-35)	(11-32)	(14-38)	

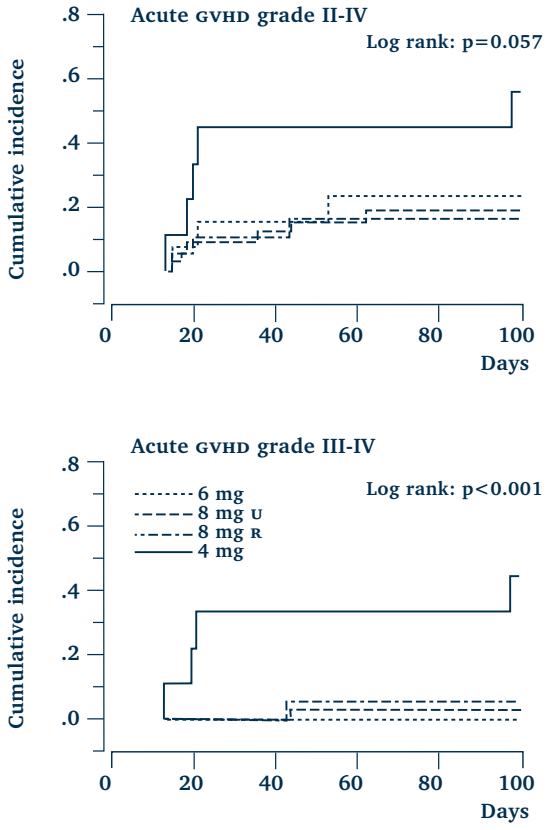
Table 3 Cumulative incidence of acute and chronic GVHD

	MUD group 1 (n=33)	MUD group 2 (n=19)	MUD group 3 (n=13)	MUD group 4 (n=9)	P
ATG dose	8 mg/kg	8 mg/kg	6 mg/kg	4 mg/kg	
aGVHD, %					
II-IV (SE)	18 (7)	16 (8)	23 (12)	56 (17)	0.057
III-IV (SE)	3 (3)	5 (5)	0	44 (17)	<0.001
cGVHD, %					
Any (SE)	24 (7)	26 (10)	23 (12)	44 (17)	ns
Ext (SE)	12 (6)	10 (7)	8 (7)	44 (17)	0.052

Any = limited and extensive.

Figure 1

Cumulative incidence of acute GVHD according to ATG dose.



from MUD group 1 and one from MUD group 4. In recipients of 8 mg/kg ATG, treated in Utrecht (MUD group 1) and Rotterdam (MUD group 2), the incidence of acute and chronic GVHD was highly comparable. A further decrease in ATG dose to 6 mg/kg (MUD group 3) did not significantly increase the rate of acute and chronic GVHD. In the group receiving 4 mg/kg ATG (MUD group 4) 44% of patients developed severe acute GVHD (grade III-IV) and extensive chronic GVHD.

After univariate analyses, no impact of other known risk factors (older age, high-risk disease status, CD3+ and CD34+ cell counts in grafts, positive recipient CMV serostatus, male recipient with female donor, use of an one HLA antigen mismatched graft) on occurrence of GVHD was found. Therefore, multivariate analyses were not performed. Furthermore, data were analysed for centre effect, which could be excluded.

Overall survival and transplant and relapse related mortality (Table 4). Median follow up was 27 (range:17-46), 28 (range:19-38), 11 (range:11-14) and 16 months (range:16-17) for group 1, 2, 3 and 4, respectively. OS and cumulative incidence of TRM and RRM at one year post-transplant are depicted in Table 4.

A higher dose of ATG did not result in an increased TRM nor RRM. One has to remind, when interpreting these data, that patient numbers in group 3 and 4 are very small.

Table 4 Overall survival and cumulative incidence of transplant and relapse related mortality at 1 year post-transplant

	MUD group 1 (n=33)	MUD group 2 (n=19)	MUD group 3 (n=13)	MUD group 4 (n=9)	P
OS, % (SE)	64 (8)	79 (18)	38 (13)	56 (34)	ns
TRM, % (SE)	12 (6)	21 (18)	23 (12)	33 (32)	ns
RRM, % (SE)	24 (14)	0	38 (26)	11 (20)	ns

OS = overall survival; TRM = transplant related mortality; RRM = relapse related mortality; SE = standard error.

Discussion

In this study, we set out to evaluate the effect of 3 different ATG doses (8 mg/kg, 6 mg/kg and 4 mg/kg) on graft failure and incidence of acute and chronic GVHD among MUD recipients of partially TCD grafts. ATG was infused pre-transplant, resulting in in-vivo TCD. Lowering ATG dose from 8 mg/kg to 6 mg/kg did not influence the occurrence of graft failure nor the incidence of GVHD. However, when ATG dose was decreased to 4 mg/kg the incidence of severe acute GVHD grade III-IV and extensive chronic GVHD rose significantly. Low-dose ATG (4 mg/kg) did not affect the incidence of graft failure, suggesting that adequate host immune suppression was achieved.

The effectiveness of ATG (Thymoglobulin™, Sangstat) as prophylaxis of GVHD in recipients of MUD grafts has been described by others[8-12]. In these studies, no in-vitro TCD of grafts was performed and prophylaxis of GVHD consisted of ATG, cyclosporine A and a short-course of methotrexate. The incidence of acute (grade III-IV) and chronic GVHD was highly variable (see Table 5). A dose-response effect was only seen in individual studies, but not between the varying studies. The results of our study are very favourable compared to those described in Table 5, as long as 6-8 mg/kg ATG was used. In other studies[14-18] ATG was derived from a different company (Fresenius). ATG-Fresenius is not equipotent to ATG

Table 5 Effect of ATG on incidence of acute and chronic GVHD

ATG dose (Thymoglobulin™, Sangstat)	Acute GVHD, grade III-IV	Chronic GVHD
15 mg/kg	11%[8]	41%[8]
	7%[9]	0%[9]
7,5 mg/kg	41%[8]	55%[8]
	38%[9]	27%[9]
4,5 mg/kg	0%[10]	27%[10]
	3%[11]*	38%[11]*
	10%[12]	44%[12]
no ATG	54%[10]	57%[10]

* In this report data are presented from recipients of matched related donor grafts (n=42) and alternative donor grafts (n=28), subgroup analysis showed no difference; superscript numbers are references.

(Thymoglobulin™, Sangstat) as used in our study. This makes a direct dose-response comparison between these and our study impossible.

Recently we reported high-dose ATG (20 mg/kg), used before 1999, to be associated with a highly increased incidence of fatal infectious complications compared to intermediate-dose ATG (8 mg/kg) used after 1999[20,21]. Furthermore, total lymphocyte, CD3+ and CD4+ T cell reconstitution was significantly lower in transplant recipients of unrelated grafts treated with high-dose ATG (15 mg/kg) compared with intermediate-dose ATG (7,5 mg/kg)[9]. Another drawback of ATG treatment is a possible increased relapse incidence[8-10,] although this is not supported by data from recent studies of Kroger et al[17] and Duggan et al[12] in which ATG was very effective in reducing the incidence of GVHD without affecting the relapse rate. Duggan et al[12] compared incidence of GVHD, relapse, TRM, OS and disease free survival in recipients of un-manipulated MUD transplants with outcome in recipients of un-manipulated matched related donor grafts. All patients received GVHD prophylaxis consisting of cyclosporine A and short-course methotrexate, while MUD recipients were also treated with low-dose (4,5 mg/kg) ATG given pre-transplant over 3 days. Outcome was highly comparable in both groups. Relapse incidence at 3 years was 45% (SE 7%) in the MUD group and 42% (SE 7%) in the matched unrelated donor group.

In the current study, the highest dose of ATG (8 mg/kg) did not result in an increased TRM nor RRM. However, patient numbers in group 3 and 4 are very small, therefore, these data should be interpreted with caution.

Considering the immunosuppressive and direct toxic effects of high-dose (15-20 mg/kg) ATG, a dose reduction is mandatory. In the setting of SCT with (partially) TCD grafts from MUDs, using limited post-transplant immunosuppression with cyclosporine A, we recommend the use of ATG in a total dose of 6-8 mg/kg.

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