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Adult Recipients of Matched Related Donor Blood Cell Transplants Given Myeloablative Regimens Including Pretransplant Antithymocyte Globulin Have Lower Mortality Related to Graft-versus-Host Disease: A Matched Pair Analysis

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ABSTRACT

Because pretransplantation anti-thymocyte globulin (ATG) seems to reduce graft-versus-host-disease (GVHD) and treatment-related mortality (TRM) after unrelated donor bone marrow transplantation (BMT), we investigated this agent in matched related donor (MRD) blood cell transplantation (BCT). Fifty-four adults receiving rabbit ATG, cyclosporine A, and methotrexate with myeloablative conditioning and undergoing first MRD BCT were matched for disease and stage with 54 patients not given ATG. Most ATG-treated patients had fludarabine with oral (7) or i.v. busulfan (46) with total body irradiation (TBI) in 10. Control patients largely received TBI with VP16 (28) or oral busulfan with cyclophosphamide (15) or fludarabine (7). The ATG was given at a total dose of 4.5 mg/kg over 3 d, finishing on day 0. Rates of acute GVHD (aGVHD) grade II-IV, aGVHD grade III-IV, and chronic GVHD (cGVHD) were 19 ± 5% versus 32 ± 6% (P = .1), 6 ± 3% versus 13 ± 5% (P = NS), and 55 ± 8% versus 96 ± 3% (P = .002) in the ATG and control groups, respectively. Patients given ATG had fewer sites involved by cGVHD compared with the control group (mean 2.1 ± 0.2 versus 2.8 ± 0.2, P = .04). Non-relapse mortality (NRM) with and without ATG, respectively, was 4 ± 3% versus 17 ± 5% at 100 d and 9 ± 4% versus 34 ± 7% at 4 yr (P = .002). Deaths were GVHD related in 3 ATG-treated patients versus 14 controls (P = .007). Despite a trend to more relapse with ATG (43 ± 7% versus 22 ± 7% at 4 yr, P = 0.05), survival was 66 ± 7% in the patients given ATG versus 50 ± 7% in the controls (P = 0.046). This study indicates that myeloablative regimens incorporating fludarabine and oral or i.v. busulfan with pretransplantation ATG given to recipients undergoing MRD BCT may result in less cGVHD, lower TRM, and probably improved quality of life in survivors compared with previous protocols.

KEY WORDS

Blood cell transplantation • Matched related • cGVHD • ATG

INTRODUCTION

GVHD, acute (aGVHD) and chronic (cGVHD), remains the major cause of morbidity and mortality after allogeneic stem cell transplantation (SCT). In general, transplants from unrelated donors (UDs) have been more troublesome in this respect. Pretransplantation serotherapy with anti-thymocyte globulin (ATG) or other antibodies appears to reduce GVHD and mortality of closely matched UD bone marrow transplantation (BMT) to levels comparable to matched related donor (MRD) BMT [1-10]. Although the move from BM to blood as a stem cell source in MRD SCT has improved some outcomes, the incidence of cGVHD in particular is higher [11,12]. It therefore seemed rational to investigate the use of

Table 1. *Diagnoses of Each Group*

	Active Leukemia		
	Standard Risk	Intermediate Risk	High Risk
AML	16 CR1	2 CR2	7 from MDS; 3 pif, 1 ref, 1 rel
ALL	6 CR1	1 CR2	1 ref, 1 rel
CML		2 (AP/CP2)	
CLL		3 rel/ref	
NHL		8 rel/ref (2 mantle cell,4 low grade, 1 intermediate grade, 1 high grade)	
MM		2	
Total	22	18	14

MDS indicates myelodysplasia; pif, primary induction failure; ref, refractory; rel, relapsed; MM, multiple myeloma.

ATG in MRD BCT. Since 1999 we have used rabbit ATG during the pretransplantation conditioning protocol for all such transplantations. We report a matched pair analysis comparing outcomes of patients receiving MRD BCT with and without ATG.

METHODS

Patients

Eighty-two adults were treated with a first myeloablative BCT and pretransplantation ATG from January 1999 until May 2002. An attempt was made to match each consecutive ATG recipient with a BCT recipient in the transplant database with the same diagnosis and disease stage but not given ATG. The database was searched backward from December 1998 until the first match was found, and this patient was then moved to the control group. The process was repeated until there was no match for a given ATG recipient. Fifty-four ATG recipients were matched with 54 control patients from a total of 82 BCT recipients not given ATG. The diagnoses of the 2 groups are recorded in Table 1. There were no patients with chronic myelogenous leukemia (CML) in first chronic phase because BM was always used for this diagnosis. Table 2 presents other details of patients and their treatments. Analysis took place in June 2006 at which time surviving ATG recipients had been followed for 49–89 mo (median, 72 mo) and control patients for 90–137 mo (median, 110 mo).

Treatment

From 1996 donors were given a fixed number of full vials of granulocyte-macrophage colony stimulating factor (GM-CSF) to provide a dose of 7.5-10 mg/kg for 4 d. Progenitor cells were collected on day 4 usually in a single procedure. Before 1996 donors took part in a dose-finding study of GM-CSF [13].

Supportive care was similar for all patients. No protective isolation was used [14]. Single-donor platelets were given to maintain counts $>10 \times 10^9$/L and RBCs to keep hemoglobin levels >80 g/L. Growth factors were not given routinely. Antibacterial and antipneumocystis prophylaxes comprised ciprofloxacin 500 mg 2 times daily and twice weekly trimethoprim/sulfamethoxazole. Blood products were all from cytomegalovirus (CMV)-seronegative donors. Before 2000 ganciclovir was given to patients who were CMV antibody positive and/or had an antibody-positive donor on clinical suspicion of CMV disease

Table 2. *Patient and Treatment Characteristics*

	ATG	No ATG
Median age (range)	42 (18-63)	41 (22-54)
Conditioning		
VP16 60 mg/kg + TBI 1200 cGy	1	26
VP16 60 mg/kg + TBI 500 cGy		2
Cyclophosphamide 120 mg/kg + TBI 1200 cGy		2
Cyclophosphamide 180 mg/kg + TBI 1200 cGy		2
Busulfan 4 mg/kg orally × 4 + cyclophosphamide 120 mg/kg		15
Busulfan 4 mg/kg orally × 4 + fludarabine 50 mg/m^2 × 5	7	7
Busulfan 3.2 mg/kg i.v. × 4 + fludarabine 50 mg/m^2 × 5	36	
Busulfan 3.2 mg/kg i.v. × 4 + fludarabine 50 mg/m^2 × 5 + TBI 400 cGy	10	
Donor/recipient sex		
Male/male	19	19
Male/female	11	15
Female/male	10	12
Female/female	14	8
Donor/recipient CMV status		
−/−	9	12
−/+	9	11
+/−	10	11
+/+	26	20

VP16 indicates etoposide.

with evidence of reactivation on serology and/or culture. After this time a policy of surveillance for pp65 antigen and preemptive therapy with ganciclovir was instituted. The aGVHD prophylaxis protocol included cyclosporin A (CSA) orally or i.v. twice daily to maintain blood levels at 250–400 μmol/L. Methotrexate was given in doses of 15 mg/m^2 i.v. on day 1 and 10 mg/m^2 on days 3, 6, and 11. Folinic acid 5 mg i.v. or orally was started 24 h after each dose of methotrexate and continued every 6 h until 12 h before the next dose [15]. The study group received rabbit ATG (Thymoglobulin, Genzyme, Cambridge, Mass) 4.5 mg/kg i.v. in divided doses over 3 d. To reduce reactions patients received 0.5 mg/kg on the first infusion followed by 2 doses of 2 mg/kg. Each dose was given as a continuous infusion over 4-8 h. The final infusion was given on the day of transplantation. Premedication included methylprednisolone 40 mg i.v. every 12 h for 6 doses and Benadryl 50 mg i.v. before each dose of ATG.

If no aGVHD occurred CSA was tapered over 4-8 wk with the intent to discontinue by 2-4 mo.

Engraftment

Daily blood cell counts were done until discharge, with BM aspirations at 3 mo for surviving patients and as clinically indicated. Granulocyte engraftment was defined as a count $>0.5 \times 10^9$/L. The platelet count needed to be $>20 \times 10^9$/L without transfusion for 3 d. Patients dying within 28 d were considered unevaluable for engraftment. Failure of neutrophil and platelet levels to recover by day 42 in the absence of persistent malignancy or other apparent cause was considered graft failure.

Graft-versus-Host Disease

Acute GVHD was graded according to standard criteria [16]. Diagnosis of cGVHD was consistent with a recently published consensus document [17]. Diagnosis and grading was performed by physicians at onset and during treatment, with later confirmation and recording by data managers.

Death was considered to be related to GVHD if it occurred during treatment for GVHD and when the primary cause was infection or GVHD.

Acute GVHD was treated with prednisone or methylprednisolone initially while continuing CSA. First-line therapy for steroid-resistant aGVHD was Thymoglobulin 2 mg/kg every other day for 2-4 doses while CSA was withheld. Chronic GVHD was treated with prednisone with or without CSA with introduction of other agents if response was incomplete.

Statistical Analysis

Fisher exact test was applied to distribution of numerical differences between groups and 2-tailed *t* test test for comparison of means.

Distributions of time to events were plotted on Kaplan-Meier curves and compared using the log-rank test, with patients being censored for relapse for estimation of nonrelapse mortality. For time to onset of cGVHD, patients were censored at time of death, DLI, or second transplantation. Analysis of time on treatment for cGVHD censored patients at relapse (if immunosuppression was deliberately stopped at this point) or death. Analysis was performed on a Macintosh computer using GraphPad Prism (GraphPad Corp, San Diego, Calif). *P* values of .05-.1 are referred to as trends and those <.05 as significant.

RESULTS

Immediate Toxicity

Despite premedication the first infusion of ATG was frequently accompanied by fever and chills. There were no severe immediate sequelae and serum sickness was not seen. Reactions were generally absent or less severe with the second and third doses.

Engraftment

One ATG recipient was not evaluable for engraftment because of early death. All other patients underwent engraftment with neutrophils, and median time to recovery was 16 d (range, 11–97 d) for ATG recipients versus 15 d (range, 10–27 d) for controls. One additional ATG recipient failed to achieve platelet recovery before death from GVHD on day 50. Platelets never decreased $<20 \times 10^9$/L in 4 ATG recipients. Death on days 39–105 occurred before platelet recovery in 5 control patients and was attributed to persistent leukemia in 1 and transplant-related causes in 4. In the remaining patients, platelets recovered in a median of 17 d (range, 8–106 d) for ATG recipients versus 16 d (range 11–109 d) for controls.

Graft-versus-Host Disease

The actuarial incidence of aGVHD grades II-IV was 19 ± 5% in ATG recipients compared with 32 ± 6% in controls (P = .1; Figure 1A). The figures for grade III-IV disease were 6 ± 3% and 13 ± 5%, respectively (P = NS; Figure 1B). Of 44 ATG recipients with grade 0-I aGVHD, 38 lived >150 d. Twenty-five discontinued CSA at 44–890 d (median, 81 d) and 13 developed cGVHD while still on CSA. Of 37 control patients with grade 0-I aGVHD, 30 lived >150 d. Of these, 9 stopped CSA at 62–175 d (median, 104 d), and 21 developed cGVHD while still taking CSA.

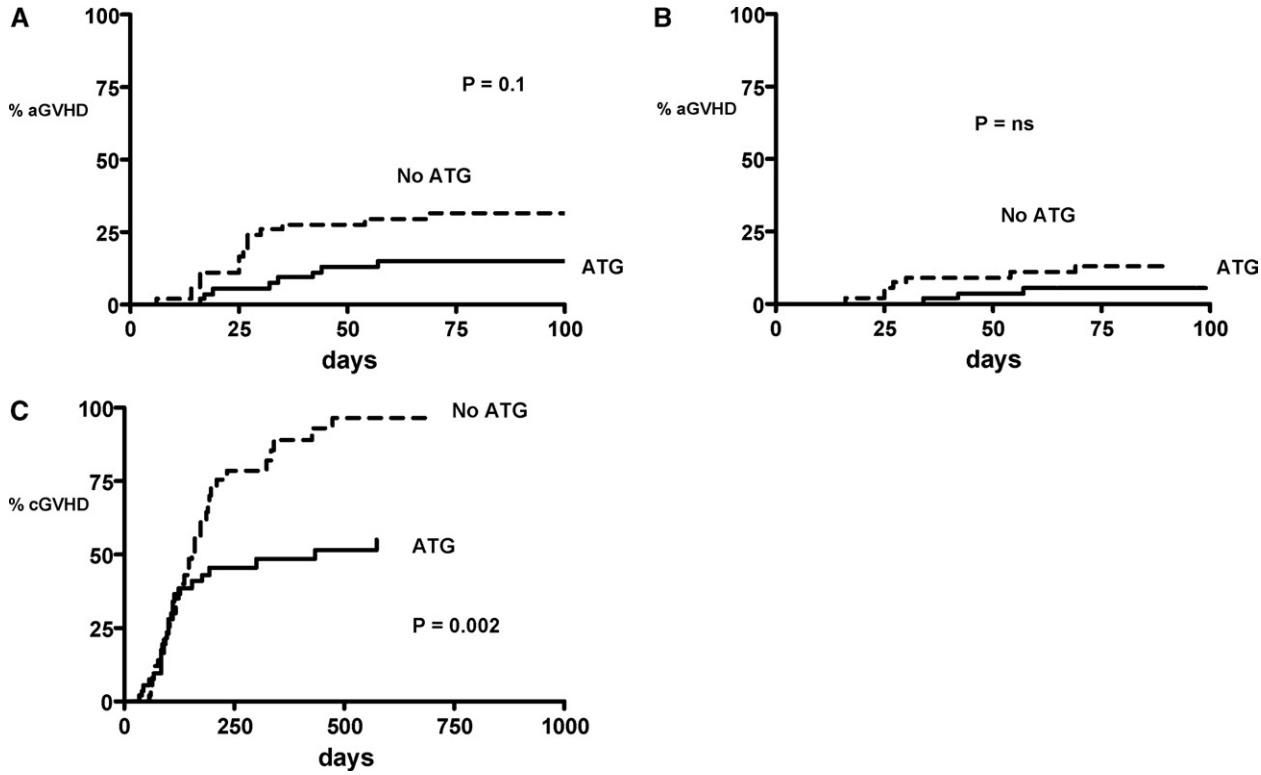

Figure 1. Kaplan-Meier plots of (A) aGVHD grades II-IV, (B) aGVHD grades III-IV, and (C) cGVHD.

Incidence of cGVHD at 2 yr was 55 ± 8% with ATG versus 96 ± 3% without ATG (P = .002; Figure 1c). Figure 2 shows the major sites of involvement by cGVHD. ATG recipients had fewer sites involved than did the control group (mean, 2.1 ± 0.2 versus 2.8 ± 0.2, P = .04). Those ATG patients with cGVHD were treated for a median of 393 d compared with 473 d for controls (P = NS; Figure 3).

Relapse

Relapse rate at 4 yr was 43 ± 7% for ATG recipients and 22 ± 7% in controls (P = .053; Figure 4A). Eight of 23 relapsing patients in the ATG group survived having achieved another remission (4) or disease stabilization (4) after more treatment. One of 12 control patients who relapsed is currently alive in remission after a second SCT.

Transplant-Related Mortality

Non-relapse mortality (NRM) was 4 ± 3% versus 17 ± 5% at 100 d and 9 ± 4% versus 34 ± 7% at 4 yr (P = .002) with and without ATG, respectively (Figure 4B). Deaths were related to GVHD in 3 ATG-treated patients versus 14 controls (P = .007). Table 3 presents the causes of early and later transplant-re-

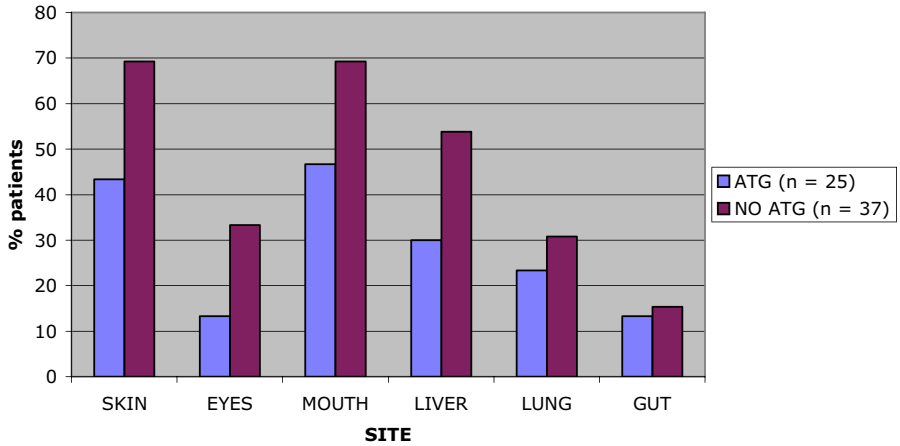

Figure 2. Distribution of cGVHD.

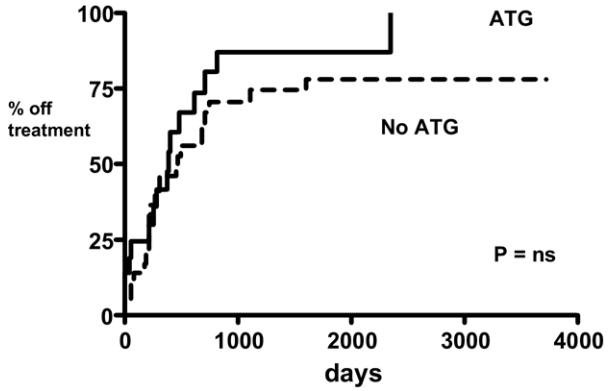

Figure 3. Kaplan-Meier plot of time to discontinuing treatment of cGVHD.

lated deaths. In the control group 4-yr TRM was 30 ± 8% in 32 TBI recipients compared with 41 ± 11% in 22 patients not given TBI (P = NS). Three of 7 patients given fludarabine with oral busulfan without ATG died of treatment-related causes.

DFS and Overall Survival

Projected disease-free survival (DFS) at 5 yr with and without ATG was 50 ± 7% versus 49 ± 7% (P = NS; Figure 5A) and survival was 66 ± 7% versus 50 ± 7%, respectively (P = .046; Figure 5B).

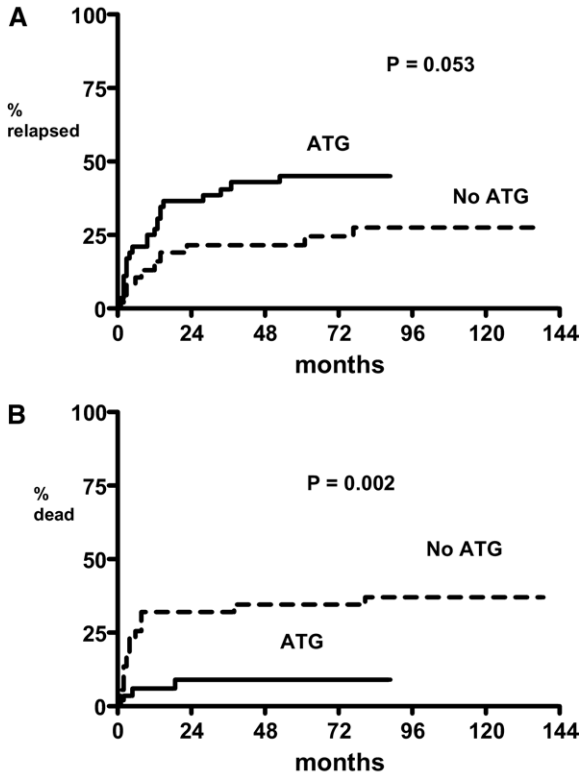

Figure 4. Kaplan-Meier plots of (A) relapse and (B) nonrelapse mortalities.

Table 3. *Causes of Nonrelapse Death*

	Death before Day 100*	Death after Day 100*	Total Deaths
ATG (n = 54)	Myocardial infarct (1), aGVHD related (1)	cGVHD related (2)	4
No ATG (n = 54)	aGVHD related (7; 1 aspergillus), interstitial pneumonitis (1), cardiac failure/ pulmonary embolus (1)	cGVHD related (7; 2 aspergillus), pneumonia (1), cerebrovascular accident (1)	21

*Includes identified opportunistic infection when death was related to GVHD.

DISCUSSION

One of the most significant changes in the practice of SCT in the past decade has been the increased use of blood as the stem cell source [11,12]. This trend is justified by the results of randomized studies indicating a survival advantage for BCT in some patient subgroups [18-23]. However, the price for this may be a significantly increased risk of cGVHD [11,12]. Therefore, not only is GVHD still the main cause of death after BCT but also the quality of life of those patients who do survive may be worse in general than that after BMT. We previously reported that unrelated BMT recipients given additional ATG have out-

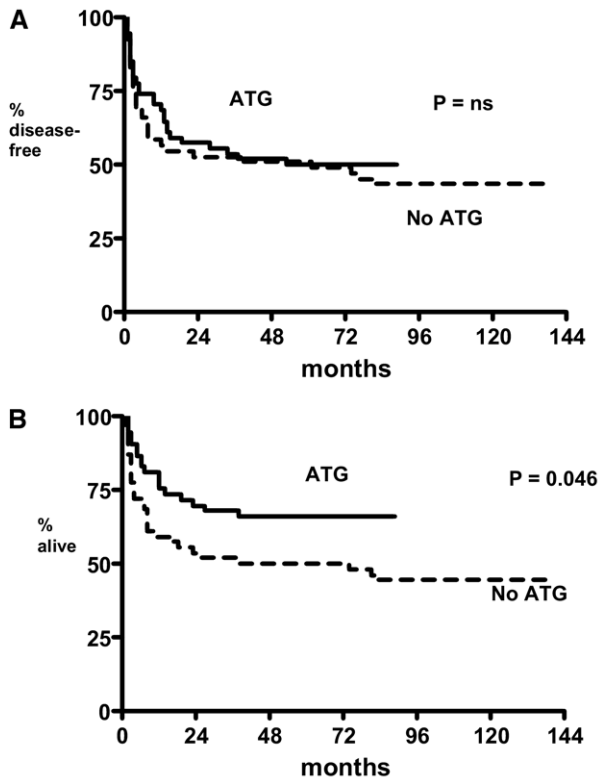

Figure 5. Kaplan-Meier plots of (A) DFS and (B) overall survival.

comes similar in every respect to MRD BMT patients receiving methotrexate/CSA alone [10]. Since 1999 all MRD SCT recipients have received ATG in an attempt to reduce morbidity and mortality from GVHD. The current study indicates some success in this respect, although the incidence of cGVHD is still substantial in ATG-treated patients. We have seen higher rates of cGVHD after BCT without ATG than reported elsewhere [24]. Explanations could include differences in managing immune suppression and/or a lower threshold for clinical diagnosis. The lower incidence of cGVHD with ATG does not seem to result from differences in rates of CSA taper; most control patients developed cGVHD while still on their initial course of CSA. The control patients also had more sites involved by cGVHD but duration of treatment was similar. Although formal assessments were not done, it is likely that overall quality of life was better in ATG recipients. Even without an effect on survival, there would therefore be an overall benefit of ATG given in this way.

ATG seemed to influence death from aGVHD and cGVHD equally. Is it also likely that improved treatment of GVHD may contribute to the lower TRM? We have little evidence to indicate that we have significantly better treatments for GVHD than were previously available and our management of this complication did not change significantly over the study period.

The tendency to more relapse is compensated for by reduced TRM leading to similar DFS figures. Some of those patients who survive long enough to relapse may be rescued by further treatment, a likely explanation for the improved overall survival. The effect on relapse is seen despite a thymoglobulin dose somewhat lower than has been customary for UD transplantations so there may be no advantage in increasing it. It would be preferable to prevent relapse if it were possible without sacrificing the benefits of ATG in ameliorating the effects of GVHD. Conceivably the improved tolerability of the current regimen could allow some dose intensification of the cytotoxic agents. Thus addition of 400-cGy TBI to the fludarabine and busulfan regimen may decrease relapse in acute myelogenous leukemia (AML) without increasing TRM [25].

The concern that ATG might result in excessive immune suppression causing post-transplantation lymphoproliferative disease and opportunistic infection has not been justified. We saw no cases of post-transplantation lymphoproliferative disease and significant morbidity and mortality from opportunistic infection were seen only in the context of GVHD.

Some shortcomings of this study must be addressed. First, it was necessary to search our data base back to December 1994 to find as many patients as possible for the matched control group. We have no evidence that outcomes of MRD transplantations changed significantly between 1994 and 1998 [14]. Over the study period support protocols changed little apart from those for CMV, but there were no deaths attributed to CMV in either group.

Acute GVHD and cGVHD may be influenced by preparative regimens and it is possible that this could explain some of our findings. More patients in the control group received full-dose, ie, 1200 cGy, TBI and most ATG-treated patients received i.v. busulfan, which gives more predictable drug exposures and is better tolerated than the oral form [26,27]. The patients in our control group given TBI developed no more TRM than did those receiving chemotherapy alone. Thus the improved TRM in the ATG group is unlikely to be from more control patients receiving TBI compared with oral busulfan. Could the use of i.v. busulfan in the ATG group have contributed to the improved outcomes? Some of the benefits of the i.v. form appear to be from a reduction in veno-occlusive disease, which was not a serious issue in our control patients. In our experience the regimen-related toxicity has been similar with i.v. or oral busulfan, with the exception of stomatitis, which seems somewhat less with the i.v. drug [28]. de Lima et al [29] reported that an almost identical regimen to the one used in the current study but without ATG was exceptionally well tolerated. It therefore remains possible that the i.v. busulfan contributed to the reduced GVHD and TRM by exposing fewer busulfan-treated patients to toxic drug levels. What influence may replacing cyclophosphamide with fludarabine have had? Combinations of oral busulfan with cyclophosphamide or fludarabine have had similar toxicities in our hands [28,30]. Three of 7 patients given fludarabine with oral busulfan without ATG died of treatment-related causes in this study, circumstantial evidence that the substitution of cyclophosphamide by fludarabine did not contribute significantly to the improved outcomes in ATG recipients.

A recent analysis compared outcomes of patients treated in Calgary with the daily i.v. busulfan/fludarabine regimen and ATG with matched controls given busulfan/cyclophosphamide from the CIBMTR database. A significant ($P = .003$) survival benefit was documented for the fludarabine/busulfan group, largely attributable to lower TRM [31]. This study showed a very significant ($P < .0001$) reduction in aGVHD in the ATG-treated patients but no influence on cGVHD. Although there was less aGVHD in our ATG-treated group, this did not reach significance, perhaps partly because of small patient numbers. The difference in the effect on cGVHD is difficult to explain. As noted above, the incidence of cGVHD in our control patients was high but consistent with our previous experience.

A recent Italian study has documented a very significant effect of thymoglobulin on morbidity and mortality from cGVHD in unrelated BMT recipients, a finding consistent with ours [32]. In addition, Deeg et al [33] demonstrated a reduction in aGVHD and cGVHD in myelodysplasia patients given Thymoglobulin before MRD transplantation without a significant effect on DFS compared with concurrently treated controls [33].

In conclusion we suggest that regimens based on fludarabine and oral or i.v. busulfan with pretransplantation ATG added to methotrexate and CSA for recipients of MRD BCT may result in less cGVHD, lower TRM, and probably improved quality of life in survivors compared with previous protocols. The challenge of relapse remains.

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