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Lower Dose of Antithymocyte Globulin (ATG) does not increase Graft-vs-Host Disease (GVHD) in Patients Undergoing Reduced-Intensity Conditioning (RIC) Allogeneic Hematopoietic Stem Cell Transplant (allo HSCT)

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Abstract

The appropriate dose of antithymocyte globulin (ATG) been utilized in reduced-intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation (alloHSCT) is yet unknown. We retrospectively compared patients who received 7.5 mg/kg (R-ATG – 39 patients) and 6 mg/kg (r-ATG- 97 patients). The cumulative incidences of acute graft-versus-host-disease (aGVHD) grade II–IV at 180 days were 46% and 41% and aGVHD grade III–IV were 11% and 18% in r-ATG and R-ATG, respectively ($P>0.30$). The respective estimated cumulative incidences at 24 months of cGVHD were 42% and 44% ($P>0.3$). There was no significant difference in non-relapse mortality ($p=0.22$), cumulative incidence of relapse ($p=0.53$), progression-free survival ($p=0.69$) or overall survival ($p=0.95$). In conclusion, a decreased ATG dose of 6 mg/kg was associated with a similar proportion of GVHD as 7.5 mg/kg ATG. Given the increasing number of RIC HSCT performed worldwide, the correct dose and preparation of ATG should be defined by prospective randomized trials.

Keywords

Antithymocyte globulin; Allogeneic Transplantation; Reduce Intensity conditioning

Introduction

Allogeneic Hematopoietic stem cell transplantation (alloHSCT) remains a viable option and offers a chance to cure many patients with hematologic malignancies as well as certain benign conditions. However, graft-versus-host disease (GVHD) remains the leading cause of non-relapse morbidity and mortality following alloHSCT^{1–7}. In recent years, reduced intensity conditioning (RIC) regimens have demonstrated decreased treatment-related

mortality (TRM) in part due to decreased acute GVHD (aGVHD), with little impact on the incidence of chronic GVHD (cGVHD)^{5,8–12}. To decrease the incidence of GVHD, in vivo T-cell depletion using antithymocyte globulin (ATG) has been added to a calcineurin inhibitor and methotrexate GVHD prophylaxis^{7,13,14}. Multiple studies have utilized one of the three commercially available preparations of ATG (Thymoglobulin, ATGAM, and ATG-Fresenius) to decrease the incidence as well as severity of acute and chronic GVHD^{7,14–17}. A randomized phase III trial comparing methotrexate and cyclosporine with and without ATG-Fresenius as GVHD prophylaxis in patients undergoing ablative alloHSCT showed a decreased incidence of chronic GVHD without an increase in mortality using a dose of 60 mg/kg⁷. Different doses of ATG Thymoglobulin, using 7.5 mg/kg and 15 mg/kg versus no ATG revealed less extensive cGVHD but increased infections at 15 mg/kg¹³. Similarly, a much lower ATG dose of 2.5 mg/kg was associated with a higher risk of aGVHD¹⁸. Hence there might be some level between 2.5–7.5 mg/kg that might be optimal. This optimal dosing of ATG is yet to be defined in part due to use of various preparations and doses of ATG in clinical trials as well as institutional preferences.

Our previous retrospective analysis (n=72) suggested that the rabbit ATG dose can be lowered from 7.5 mg/kg to 6 mg/kg without increasing GVHD, prolonging time to engraftment, or changing donor chimerism¹⁶. With the lower dose of ATG, we also showed improved non-relapse mortality, decreased frequency of CMV reactivation, and decreased bacterial infections. Herein, we update our previous analysis on patients undergoing RIC allo HSCT with three times the number of patients receiving low dose ATG and additional follow-up.

Patients and Methods

Study design

One hundred thirty six consecutive patients with hematologic malignancies who underwent RIC alloHSCT with fludarabine, busulfan and rabbit ATG preparatory regimen between January 2006 and December 2010 were analyzed. The study was approved by the cancer institutional review board at the Ohio State University.

Conditioning regimen

The condition regimen consisted of intravenous (IV) fludarabine 30 mg/m²/day over 30 minutes on days –7 to –3 (total dose, 150 mg/m²) and IV busulfan 0.8 mg/kg/dose over 2 hours every 6 hours for 8 doses on days –4 to –3 (total busulfan dose, 6.4 mg/kg). In the first group (high dose ATG, R-ATG), 39 consecutive patients received rabbit ATG (Thymoglobulin®, Genzyme; Cambridge, MA) at a dose of 2.5 mg/kg/day over 6 hours on days –4 to –2 (total ATG dose, 7.5 mg/kg) from January 2006 to September 2007. In the second group (low dose ATG, r-ATG), the ATG dose was lowered starting Oct-2007 as part of a quality improvement effort and 97 patients received rabbit ATG at 2 mg/kg/day on days –4 to –2 (total ATG dose, 6 mg/kg) through December 2010.

GVHD prophylaxis

Standard pharmacological prophylaxis for GVHD included intravenous tacrolimus 0.03 mg/kg/day starting on day -2 and methotrexate 5 mg/m² on days +1, +3, +6 and +11. Oral tacrolimus was started around neutrophil engraftment. Tacrolimus blood levels were monitored initially twice weekly and then weekly until day +100 to maintain levels between 8–12 ng/mL.

Supportive care

Prophylaxis against fungal infection consisted of fluconazole, voriconazole or posaconazole initiated on day -1 and continued until day +100 unless continuation of therapy was clinically indicated in accordance with institutional standard. Antiviral prophylaxis consisted of oral valacyclovir for herpes infections and TMP-SMX or dapsone for *Pneumocystis jiroveci*. Both medications were continued until patients were off immunosuppressive therapy and CD4+ count was > 200. Routine CMV prophylaxis was not utilized. Preemptive screening for CMV infection consisted of weekly CMV monitoring by serum quantitative PCR beginning on admission and until day +100 or longer as dictated by the clinical course. Treatment was initiated when the PCR indicated > 4000 copies/mL and outpatient treatment consisted of Valganciclovir 900 mg twice daily until CMV was undetectable by PCR. Monitoring of EBV was done weekly through day +100. If serum EBV PCR levels were greater than 4000 copies/mL upon repeated measurement, patients were treated with one dose of Rituximab at 375 mg/m². Any further increase in serum EBV PCR levels were treated with three weekly doses of Rituximab for a total of 4 doses. Granulocyte-colony stimulating factor (G-CSF) was part of standard-of care treatment until September 2007 when it was excluded and only given at the discretion of the treating physician in cases of infections with neutropenia.

GVHD Assessment and Treatment

Acute GVHD was graded according to the 1994 consensus conference¹⁹. Chronic GVHD was evaluated according to limited versus extensive as previously described^{20,21}. Corticosteroid comprised the first line therapy of acute GVHD (grade II–IV) and extensive chronic GVHD. Second line treatment was at the discretion of the treating physician.

Statistical Analysis

Baseline demographic and clinical variables were compared between the two treatment cohorts using Fisher's Exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. The time of neutrophil engraftment was considered the first of 3 consecutive days with the absolute neutrophil count $\geq 0.5 \times 10^9/L$. The time of platelet engraftment was considered the first of 7 consecutive days with platelet count $\geq 20 \times 10^9/L$ without transfusion. Progression-free survival (PFS) and overall survival (OS) estimates were calculated by the Kaplan-Meier method and compared using the log-rank test. PFS was defined as the time from transplantation until progression or death, whichever occurred first. OS was defined as the time from transplantation until death. Cumulative incidence of aGVHD was evaluated within the first 180 days post transplant, whereas cGVHD was evaluated within the first 24 months post transplant given that patients were followed for at

least 100 days and without early progression or death. Cumulative incidence of aGVHD, cGVHD, relapse, and non-relapse mortality (NRM) were analyzed using Gray's test and accounting for competing risks; competing risks for aGVHD and cGVHD were relapse or death, the competing risk for relapse was death from any cause, and the competing risk for NRM was death due to disease. Cumulative incidence for infection types were evaluated within the first 180 days of transplant and also analyzed using Gray's test, where the competing risks were grade II–IV aGVHD, cGVHD, relapse, or death prior to any documented infection. For all analyses, patients without an event were censored at the time last evaluated for a particular endpoint. Multivariable models were fit using either Cox proportional hazards or Fine and Gray models. With treatment cohort in all models, other variables considered for multivariable analyses included patient age and sex, donor sex, disease group, prior autograph, degree of HLA match, Karnofsky performance status, CMV status, and stem cell dose. Models were fit using backwards selection until all variables, other than perhaps treatment cohort, were statistically significant at $\alpha = 0.05$. All p-values presented are from 2-sided tests. All analyses were conducted using SAS software version 9.3 or the cmprsk package in TIBCO Spotfire S+ version 8.2.0.

Results

Patient Characteristics

One hundred thirty six consecutive patients were included in this analysis. Thirty nine patients received high dose ATG (R-ATG, 7.5 mg/kg total) and 97 patients received low dose ATG (r-ATG, 6 mg/kg total). Baseline clinical characteristics are summarized in Table 1. As previously documented, patients with chronic myelogenous leukemia in first chronic phase, acute leukemia in first complete remission, myelodysplastic syndrome with refractory anemia, or refractory anemia with ringed sideroblasts were considered to have low-risk disease. All other patients were placed in the high-risk disease category. There were no significant differences in age, gender for both donor or recipient, KPS, degree of HLA match, number of prior autografts, donor/recipient CMV status, and CD34 cell dose between the two groups ($p > 0.15$). All but 8 patients received peripheral blood stem cells, with 87% from an unrelated donor. The distribution of hematologic diagnoses differed between treatment groups ($p = 0.02$) with a higher proportion of patients transplanted for CLL with r-ATG versus R-ATG (30% vs. 10%), whereas a lower proportion of patients with AML/MDS/NHL/HD and other histologies were transplanted with r-ATG versus R-ATG. This translated into a higher proportion of patients with high-risk disease treated with r-ATG as compared to R-ATG ($p = 0.03$).

Engraftment and Chimerism

Time to neutrophil engraftment was longer among those patients receiving r-ATG ($p = 0.002$) which may be attributed to fewer patients in the r-ATG group receiving G-CSF (38% r-ATG vs 77% R-ATG, $p < 0.0001$). Still, all patients engrafted by day 45, with half of the patients engrafting by day 17 on r-ATG and half by day 15 on R-ATG. The time to platelet engraftment and donor-cell chimerism on days +30, +90, +180 and +360 were not significantly different between the groups. Secondary graft failure occurred in 1 patient in each cohort.

Graft versus host disease

All patients were assessed for presence of grade II–IV aGVHD, and patients progression-free and surviving 100 days post transplantation were evaluable for cGVHD (n=102). There were 61 occurrences of aGVHD grade II–IV, all occurring within the first 180 days following transplant, and the cumulative incidence was not significantly different between the r-ATG and R-ATG groups ($p=0.59$; Figure 1A); cumulative incidence estimates at 180 days were 46% and 41%, respectively (Table 2). There was also no significant difference in the cumulative incidence of aGVHD grade III–IV ($p=0.31$; Figure 1B), with estimates at 180 days of 11% and 18%, respectively, in those treated with r-ATG and R-ATG (Table 2). Among those evaluable for cGVHD, there have been 43 cGVHD occurrences with no significant difference in cumulative incidence ($p=0.90$, Figure 1C); 24-month estimates were 42% and 44% in the r-ATG and R-ATG groups, respectively (Table 2). Further, there was no significant difference in cumulative incidence of extensive cGVHD ($p=0.77$, Figure 1D), with 24-month estimates of 35% and 38%, respectively in the r-ATG and R-ATG groups (Table 2). Conclusions did not change when adjusting for other important variables in multivariable analyses (model for aGVHD II–IV adjusted for disease group, degree of HLA match, and patient gender; model for aGVHD III/IV was “unadjusted” as no potential explanatory variable was significant in the model; models for cGVHD and extensive cGVHD adjusted for disease group, prior autograft, and stem cell dose). When analyses were limited to unrelated donor transplants only, conclusions regarding the lack of impact on GVHD by ATG group did not change.

Infectious Complications

There were no statistically significant differences in Bacterial infections, and CMV and EBV reactivation between the two groups up to day 180 post alloHSCT with grade II–IV aGVHD, cGVHD, relapse, or death as competing risks ($p>0.30$). This is in contrast to the previous reported increase in CMV reactivation. In this study only patients with CMV reactivation greater than 4000 and those that required treatment were included, whereas in the previous study, all patients with CMV elevation were included, thus accounting for the differences. One patient in the r-ATG group had CMV disease with resulting death from CMV encephalitis. There was however a lower cumulative incidence of BK-virus associated hemorrhagic cystitis in the r-ATG group compared with the R-ATG group ($p=0.01$, Table 3), with 180 day estimates of 3% versus 15%. No clinical characteristic was found to be significantly associated with incidence of BK-virus associated hemorrhagic cystitis, although of the 9 cases (3 r-ATG vs 6 R-ATG), eight were male and all had received stem cells from a male unrelated donor (8 PB stem cell source). Prior to any competing events, there were no cases of adenovirus infection and only one invasive fungal infection in a patient treated with r-ATG. The median number of days of initial hospitalization was 19 in both groups and no significant difference in the number of readmissions within 100 days of initial discharge from the hospital was observed ($p=0.48$). When analyses were limited to unrelated donor transplants only, conclusions did not change.

Survival and Relapse

At a median follow up of 28 months (range 10.6 to 67.3 months), 66 patients have died with the majority due to disease relapse (Table 4). Four patients (17%) in R-ATG died of a second cancer compared to none in r-ATG. There was no statistically significant difference in cumulative incidence of NRM ($p=0.22$, Figure 2A) or cumulative incidence of relapse (CIR) ($p=0.53$, figure 2B) between the treatment groups, nor were there statistically significant differences in OS or PFS (Figure 3A–B). The 24-month OS estimates were 58% and 54% and the 24-month PFS estimates were 50% and 44% respectively for the r-ATG and R-ATG groups (Table 4). Again conclusions did not change when adjusting for other significant covariates in multivariable models (model for NRM adjusted for gender mismatch between donor and patient; model for CIR adjusted for disease group; model for OS adjusted for patient gender; model for PFS adjusted for patient gender, disease group, and performance status). When analyses were limited to unrelated donor transplants only, differences in cumulative incidence of NRM became more pronounced, where cumulative incidence of NRM tended to be higher in patients receiving R-ATG. However, this did not reach statistical significance ($p=0.08$). Analyses of other clinical endpoints in this subgroup of patients resulted in conclusions similar to those obtained when including all patients.

Discussion

The optimal dose and preparation of ATG utilized with the conditioning regimen has been inconclusive. As we had previously shown¹⁶ and now with longer follow up and with more patients, the study continues to support the use of lower dose ATG. There was no statistical difference in grade II–IV aGVHD, cGVHD, relapse, NRM, PFS and OS between the two treatment groups. As a limitation of this retrospective analysis, based on the data that was collected and to be consistent with our prior publication, cGVHD was defined as GVHD occurring at least 100 days following alloHSCT. Another limitation of the study is that the NIH consensus criteria were not used in defining cGVHD²² at our institution up until 2010.

In contrast to the previously reported data by our group showing a higher incidence of CMV reactivation in the R-ATG group¹⁶, no differences in CMV reactivation are reported in this current follow-up study. In this study only patients with CMV reactivation greater than 4000 and those that required treatment were included, whereas in the previous report, all patients with CMV elevation were included, thus accounting for the differences. We however did find a higher cumulative incidence of BK-virus associated hemorrhagic cystitis in the R-ATG group versus the r-ATG group ($p=0.01$), with 180 day estimates of 15% versus 3%. This however did not translate into a longer hospital stay or risk for other infections. Another significant finding in this study was the increase use of G-CSF in the R-ATG group (77%) as compared to the r-ATG group (38%), contributing to the shorter time to neutrophil engraftment in the R-ATG group. This however did not translate to a difference in infection rates. Granulocyte-colony stimulating factor (G-CSF) was part of standard-of care treatment until September 2007 when it was excluded and only given at the discretion of the treating physician if needed.

Recent data from prospective studies supports the use of ATG as a part of a myeloablative conditioning regimen to abrogate GVHD^{7,13}. To date, there are no prospective randomized

studies which have examined the role of ATG in patients undergoing RIC HSCT. One of the largest retrospective studies evaluated outcomes in RIC HSCT utilizing *in vivo* T-cell depletion via ATG or alemtuzumab compared with no *in vivo* T-cell depletion (T cell-replete)²³. Both horse and rabbit ATG were utilized in this study. Rabbit ATG dose consisted of <6 mg/kg in 148 patients, 6–8 mg/kg in 110 patients, and >8 mg/kg in 147 patients. The results of this study showed similar rates of aGVHD II–IV between the ATG and T cell-replete groups (38% vs. 40%), but a lower rate of aGVHD II–IV with alemtuzumab (19%) ($p<0.0001$). The 3-year rate of cGVHD was lowest in the alemtuzumab group, followed by the ATG group, and highest in the T cell-replete group (24% vs. 40% vs. 52%; $p<0.0001$). However, more patients relapsed, and the disease free survival was lower in both the ATG and alemtuzumab groups when compared to T cell-replete group ($p<0.001$). The authors concluded that *in vivo* T-cell depletion should be used with caution in patients receiving RIC HSCT. A recent retrospective analysis of 1,250 patients undergoing RIC related transplant compared control patients (no *in-vivo* T cell deplete) to patients receiving ATG (<6 mg/kg or 6mg/kg) or alemtuzumab²⁴. They determined that the incidences of grade II–IV acute GVHD were 21.4, 17.6 and 10.2% in control, ATG and alemtuzumab patients, respectively ($P<0.001$). In multivariable analysis, the use of ATG and the use of alemtuzumab were each associated with a lower risk of chronic GVHD ($P<0.001$ each), but a similar risk of relapse, nonrelapse mortality, leukemia-free survival and OS as with the control group. There was however a suggestion for higher relapse risk in patients given 6 mg/kg ATG (HR=1.4, $P=0.08$). The study therefore suggested that a certain amount of *in vivo* T-cell depletion can be safely used in RIC related allo-HSCT²⁴. That “certain amount” is yet to be determined. Another concern with ATG as part of the conditioning regimen has been the demonstration of an increased cumulative incidence of post transplant lymphoproliferative disorder (PTLD) in patients with higher blood level of ATG²⁵. Podgorny et al measured blood ATG level on day 7 and 28 post-transplant in patients who received ATG thymoglobulin at a total dose of 4.5 mg/kg²⁵. Fourteen of 153 patients (9%) developed PTLT. In another prospective study by Romberger et al, 3/76 patients (4%) developed PTLT, 2 received ATG dose of 8 mg/kg and 1 patient received 6 mg/kg²⁶. However, the large, prospective study by Soiffer et al. showed that 7/797 patients (0.9%) developed PTLT in the *in vivo* T cell-depleted group (2 with alemtuzumab and 5 with ATG) vs. 2/879 patients (0.25) in the T cell-replete group with the 3-year cumulative incidence of EBV-PTLT being 2%, 2% and 0.1%, respectively ($p=0.05$)²³. In our study, 2 patients (5%) in the R-ATG group had PTLT, one with associated elevated EBV and one without any EBV positivity. There was no PTLT in the r-ATG group.

As T-cells are depleted, infectious complications, particularly viral and fungal infections, should increase²⁵. Bacigalupo et al showed an increased incidence of lethal infections in patients receiving higher doses of ATG at 15 mg/kg¹³. A retrospective study by Ayuk et al showed a decreased 2-year TRM with lower dose of ATG-F (30 mg/kg) compared to higher dose (60 mg/kg), mainly due to a higher incidence of fatal infections in the ATG-60 group²⁷. While we did not find any statistical differences in bacterial, CMV and EBV infections, there was an increase in BK-associated hemorrhagic cystitis in the R-ATG group.

Given the increasing number of RIC HSCT performed worldwide, the correct dose and preparation of ATG should be defined by prospective randomized trials. Until then, our study is additional evidence supporting the role of *in vivo* T-cell depletion with a lower dose of rabbit ATG. With the analysis of these data, as of December 1, 2013, as part of a continued quality improvement effort, we have further amended our standard of care ATG use to 4.5 mg/kg given at 2.25 mg/kg on days –3 and –2

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Figure 1.

Cumulative Incidence of GVHD according to ATG dosing. Dashed curves represent patients receiving ATG at 6.0 mg/kg (r-ATG) and solid curves represent patients receiving ATG at 7.5 mg/kg (R-ATG). (A) Cumulative incidence of grade II–IV acute GVHD. (B) Cumulative incidence of grade III–IV acute GVHD. (C) Cumulative incidence of overall chronic GVHD. (D) Cumulative incidence of extensive chronic GVHD.

Figure 2.

(A) Cumulative incidence of non-relapse mortality according to ATG dosing. (B) Cumulative incidence of relapse according to ATG dosing. Dashed curves represent patients receiving ATG at 6.0 mg/kg (r-ATG) and solid curves represent patients receiving ATG at 7.5 mg/kg (R-ATG).

Figure 3.

(A) Kaplan-Meier estimates of overall survival following reduce-intensity conditioning alloHSCT. (B) Kaplan-Meier estimates of progression-free survival following reduce-intensity conditioning alloHSCT. Dashed curves represent patients receiving ATG at 6.0 mg/kg (r-ATG) and solid curves represent patients receiving ATG at 7.5 mg/kg (R-ATG).

Table 1

Baseline Patient Characteristics at the Time of Transplantation

Patient Characteristics	r-ATG (6 mg/kg) (n=97)	R-ATG (7.5 mg/kg) (n=39)	p-value
Median age, years (range)	58 (21–73)	57 (24–69)	0.96
Age > 60, num. (%)	38 (39)	17 (44)	0.70
Age < 60, num. (%)	59 (61)	22 (56)	
Gender (donor), num. (%)			0.49
Male	78 (80)	29 (74)	
Female	19 (20)	10 (26)	
Gender (recipient), num. (%)			0.84
Male	66 (68)	28 (72)	
Female	31 (32)	11 (28)	
Diagnosis, num. (%)			0.02
AML/MDS	42 (43)	18 (46)	
NHL/Hodgkin disease	23 (24)	12 (31)	
CLL	29 (30)	4 (10)	
Other	3 (3)	5 (13)	
Disease risk *, num. (%)			0.03
Low	17 (18)	14 (36)	
High	80 (82)	25 (64)	
Prior autograft, num. (%)			0.20
No	90 (93)	33 (85)	
Yes	7 (7)	6 (15)	
Donor, num. (%)			1.00
Unrelated	84 (87)	34 (87)	
Related	13 (13)	5 (13)	
Degree of HLA match, num. (%)			0.49
8/8	0 (0)	1 (3)	
8/10	2 (2)	1 (3)	
9/10	19 (20)	8 (21)	
10/10	76 (78)	29 (74)	
KPS, num. (%)			0.58
70	2 (2)	1 (3)	
80	27 (28)	13 (33)	
90	49 (51)	21 (54)	
100	19 (20)	4 (10)	
CMV status, num. (%)			0.33

Patient Characteristics	r-ATG (6 mg/kg) (n=97)	R-ATG (7.5 mg/kg) (n=39)	p-value
Patient and/or donor +ve	58 (60)	27 (69)	
Both patient and donor –ve	39 (40)	12 (31)	
Graft source, num. (%)			0.23
Bone marrow	4 (4)	4 (10)	
Peripheral blood stem cells	93 (96)	35 (90)	
Median CD 34+ cell dose (range)	7.08 (1.68 – 12.04)	7.02 (0.69 – 10.17)	0.64

Abbreviations: AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; NHL, non-hodgkins lymphoma; CLL, chronic lymphocytic leukemia; KPS, Karnofsky performance score; CMV, cytomegalovirus.

* patients with chronic myelogenous leukemia in first chronic phase, acute leukemia in first complete remission, myelodysplastic syndrome with refractory anemia, or refractory anemia with ringed sideroblasts were considered to have low-risk disease. All other patients were placed in the high-risk disease category.

Table 2

Pattern of Graft-versus-host Disease (GVHD)

Cumulative Incidence: aGVHD	r-ATG (6 mg/kg) (n=97)	R-ATG (7.5 mg/kg) (n=39)	p-value
Grade II–IV			0.59
Number of Events	45	16	
CumInc. at Day 180 (95%CI)	0.46 (0.36–0.56)	0.41 (0.25–0.57)	
Grade III–IV			0.31
Number of Events	11	7	
CumInc. at Day 180 (95%CI)	0.11 (0.05–0.18)	0.18 (0.06–0.30)	
Limited and Extensive			0.90
Number of Events	29	14	
CumInc. at 24 months (95%CI)	0.42 (0.30–0.54)	0.44 (0.26–0.62)	
Extensive			0.77
Number of Events	24	12	
CumInc. at 24 months (95%CI)	0.35 (0.24–0.47)	0.38 (0.20–0.55)	

Abbreviations: aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease

Table 3**Infectious Complications Following Transplantation**

Characteristic	r-ATG (6 mg/kg) (N=97)	R-ATG (7.5 mg/kg) (N=39)	p-value
CMV Reactivation			0.58
Number of Events	32	11	
CumInc. at Day 180 (95% CI)	0.33 (0.24–0.42)	0.28 (0.14–0.43)	
EBV Reactivation			0.77
Number of Events	17	8	
CumInc. at Day 180 (95%CI)	0.18 (0.10–0.25)	0.21 (0.08–0.33)	
BK-virus associated hemorrhagic cystitis			0.01
Number of Events	3	6	
CumInc. at Day 180 (95%CI)	0.03 (0–0.07)	0.15 (0.04–0.27)	
Bacterial infections			0.30
Number of Events	15	9	
CumInc. at Day 180 (95%CI)	0.15 (0.08–0.23)	0.23 (0.10–0.37)	
Length of initial hospital stay (days)			0.79
Median	19	19	
Range	13–42	14–107	
Number of readmissions within 100 days post initial discharge			0.48
0	43 (44)	12 (31)	
1	33 (34)	15 (38)	
2	13 (13)	8 (21)	
3	8 (8)	4 (10)	

Abbreviations: CMV, cytomegalovirus; EBV, Epstein barr virus; CumInc, cumulative incidence.

Table 4

Survival and Relapse Post Transplantation

Outcome	r-ATG (6 mg/kg) (N=97)	R-ATG (7.5 mg/kg) (N=39)	p-value
Median follow up, months (range)	23.8 (10.6–45.3)	49.4 (31.4–67.3)	---
Non-relapse Mortality			0.22
Number of Events	16	13	
CumInc. at 24 months, (95% CI)	0.16 (0.09–0.24)	0.26 (0.12–0.40)	
Relapse			0.53
Number of Events	34	13	
CumInc. at 24 months, (95% CI)	0.35 (0.25–0.45)	0.31 (0.16–0.46)	
Progression-free Survival (PFS)			0.69
Median, months (95% CI)	22 (8)	10 (6)	
PFS at 24 months (95% CI)	0.50 (0.39)	0.44 (0.28)	
Overall Survival (OS)			0.95
Median, months (95% CI)	38 (20)	32 (9)	
OS at 24 months (95% CI)	0.58 (0.47)	0.54 (0.37)	
Cause of death, num. (%)	N = 43	N = 23	0.07
Disease	27 (63)	10 (43)	
Infection	5 (12)	4 (17)	
GVHD	6 (14)	5 (22)	
2 nd cancer	0 (0)	4 (17)	
Cardiac	1 (2)	0 (0)	
Pulmonary	1 (2)	0 (0)	
VOD	1 (2)	0 (0)	
Other	2 (5)	0 (0)	

Abbreviations: GVHD, graft-versus-host disease; VOD, veno-occlusive disease; NRM, non-relapse mortality; CI, confidence interval; NR, not reached.