Biology of Blood and Marrow Transplantation

Allogeneic − Adult

Standard Antithymocyte Globulin Dosing Results in Poorer Outcomes in Overexposed Patients after Ex Vivo CD34+ Selected Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Antithymocyte globulin (ATG) use mitigates the risk of graft rejection and graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (allo-HCT), but ATG overexposure in the setting of lymphopenia negatively affects immune recovery. We hypothesized that standard empiric weight-based dosing of ATG, used to prevent graft rejection in ex vivo CD34-selected allo-HCT, may lead to serious adverse consequences on outcomes in certain patients. We evaluated 304 patients undergoing myeloablative-conditioned ex vivo CD34-selected allo-HCT with HLA-matched donors for the treatment of hematologic malignancies. Patients received rabbit ATG at a dose of 2.5 mg/kg/day i.v. on days -3 and/or -2. An ATG dosing cutoff of 450 mg was used for statistical analyses to assess the relationship between ATG and overall survival (OS). Among all patients, median total ATG dose was 360 mg (range, 130 to 510 mg); 279 (92%) received a total dose of ATG $\leq$450 mg, and 25 (8%) received a total dose >450 mg. On the first day of ATG administration (day -3), the median absolute lymphocyte count was .0 K/μL. For patients who received a total dose of ATG >450 mg or $\leq$450 mg, the incidences of acute and late-acute GVHD grade II-IV were statistically similar. At 3 years post-HCT, for patients who received a total dose of ATG >450 mg or $\leq$450 mg, nonrelapse mortality (NRM) rates were 35% and 18%, respectively (P = .029), disease-free survival (DFS) rates were 37% and 61%, respectively (P = .003), and OS rates were 40% and 67%, respectively (P = .001). Among all patient and HCT characteristics in multivariable analyses, receipt of a total dose of ATG >450 mg was associated with an increased risk of NRM (hazard ratio [HR], 2.9; P = .01), shorter DFS (HR, 2.0; P = .03), and inferior OS (HR, 2.1; P = .01). In summary, the use of weight-based ATG at a time of relative lymphopenia before ex vivo CD34-selected allo-HCT results in overdosing in heavier patients, leading to higher NRM and lower DFS and OS. Further pharmacokinetic investigation in this setting is critical to determining the optimal dosing strategy for ATG.

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INTRODUCTION

Numerous studies have demonstrated that antithymocyte globulin (ATG) integrated into conditioning regimens as a method of in vivo T cell depletion reduces the risks of acute and chronic graft-versus-host disease (GVHD) after conventional and umbilical cord blood allogeneic hematopoietic cell transplantation (allo-HCT) [1-6]. The efficacy of ATG may come at the cost of increased risk of certain infections and disease relapse depending on the HCT population studied [1,2,7-10]. These variable outcomes associated with ATG are related to its polyclonal and multitargeted activity, its numerous formulations and dosing schemes, and the heterogeneous allo-HCT settings in which it is used [3].

Moreover, the appropriate peri-HCT exposure to ATG will maximize its anti-GVHD properties and minimize undesirable

effects. Recent population-based pharmacokinetic (PK) and pharmacodynamic analyses demonstrate that standard empiric weight-based dosing often results in highly variable ATG exposure that has profound effects on immune recovery, infection rates, GVHD, and disease relapse [11-14]. A patient's absolute lymphocyte count (ALC) at the time of ATG administration has emerged as the most important factor in ATG metabolism; thus, the intensity of the conditioning regimen and the timing of ATG dosing relative to allograft infusion must be considered in treatment decisions [14,15].

In ex vivo CD34-selected allo-HCT, T cell depletion markedly reduces acute and chronic GVHD rates while maintaining highly favorable anticancer efficacy. In this setting, ATG is incorporated into the conditioning regimen specifically to promote engraftment and reduce the risk of graft rejection [16-22]. It is administered to patients who have received the majority of their myeloablative conditioning and are lymphopenic. Given the current standard empiric weight-based dosing and timing of ATG administration in patients undergoing ex vivo CD34-selected allo-HCT, we hypothesized that some patients may be overexposed to ATG, leading to serious adverse consequences on outcomes.

METHODS
Study Design

We conducted a retrospective analysis in adult patients who underwent their first allo-HCT and received ex vivo T cell-depleted allografts using the CliniMACS CD34 Reagent System (Miltenyi Biotech, Gladbach, Germany) as calcineurin inhibitor-free GVHD prophylaxis. No further pharmacologic immunosuppression was used after allo-HCT. All patients were treated for acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), or non-Hodgkin lymphoma at Memorial Sloan Kettering Cancer Center (MSK) between 2006 and 2016. Patients received peripheral blood allografts from a 10/10 HLA-matched related donor (MRD) or unrelated donor (MUD) identified by high-resolution DNA sequence-specific oligonucleotide typing for HLA-A, -B, -C, -DRB1, and -DQB1 loci. Patients received a pre-HCT myeloablative conditioning regimen at the discretion of the treating physician. The chemotherapy-based conditioning was either a busulfan, melphalan, and fludarabine regimen or a clofarabine, melphalan, and thiotepa regimen. The high-dose total-body irradiation (TBI)-based conditioning (1375 cGy) was either a TBI, thiotepa, and cyclophosphamide regimen or a TBI, thiotepa, and fludarabine regimen. Patients received rabbit ATG (Thymoglobulin; Sanofi, Paris, France) at a dose of 2.5 mg/kg/day i.v. on days -3 and/or -2. All patients received supportive care, including growth factors, prevention of opportunistic infections, and sinusoidal obstruction syndrome prophylaxis according to standard MSK Adult Bone Marrow Transplant Service guidelines. This study was approved by the MSK Institutional Review Board.

Study Endpoints and Statistical Analyses

For the statistical analyses, disease entities were grouped as acute leukemias, MDS, and other hematologic malignancies, which included MPN, MDS/MPN overlap, and non-Hodgkin lymphoma. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method. The cumulative incidences of relapse, nonrelapse mortality (NRM), and GVHD were estimated using the cumulative incidence method for competing risks. Relapse and death were considered competing risks for GVHD and for NRM and relapse, respectively. The associations between patient and HCT characteristics and outcomes were evaluated using Cox proportional hazards regression models. Disease risk was assessed using the validated Disease Risk Index (DRI), and comorbidities were assessed using the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) [23,24]. Cause-specific Cox models were used for relapse, NRM, and GVHD. The final multivariable model for OS was stratified by HCT-CI and DRI to meet the proportional hazards assumption of the model. The significance threshold was set at $P < .05$.

An ATG dosing cutoff was determined by evaluating multiple methods to assess the relationship between ATG and OS: receiver operating characteristic curves for prediction of survival at fixed time points, smooth estimates of median survival as a functional of ATG dose, martingale residuals plotted from a Cox model including only age against ATG dose, and spline coefficients fitted for ATG in a Cox model providing a smooth fit and highlighting doses at increased risk (Supplementary Material). Based on these analyses, a total ATG

dose cutoff of 450 mg (corresponding to patient weight >90 kg) was selected, which included patients at increased risk of all-cause death and an adequate number who had received high ATG doses.

RESULTS
Patient and HCT Characteristics

Patient and HCT characteristics for all evaluated patients are shown in Table 1. A total of 304 patients were evaluated, and the median duration of follow-up among survivors was 49 months (range, 8 to 138 months). Neutrophil engraftment occurred in 302 patients (99.3%), and 2 patients (.7%) were unevaluable for engraftment because they died of infection, 1 on day +8 and the other on day +10. Before allo-HCT, 295 patients (97%) received 2 infusions of ATG, and 9 patients (3%) received 1 infusion of ATG. Among all patients, 279 (92%)

Table 1
Patient and Transplantation Characteristics (N = 304)

Characteristic	Value
Age, yr, median (range)	56 (20-73)
Female sex, n (%)	140 (46)
Disease, n (%)	
Acute leukemia	189 (62)
MDS	77 (25)
Other hematologic malignancy*	38 (13)
DRI, n (%)	
Low	20 (7)
Intermediate	237 (78)
High	37 (12)
Unevaluable	10 (3)
HCT-CI, n (%)	
0	62 (20)
1-2	110 (36)
≥3	132 (44)
Patient CMV serostatus, n (%)	
Seropositive	192 (63)
Seronegative	112 (37)
HLA match, n (%)	
MRD	132 (43)
MUD	172 (57)
Conditioning, n (%)	
Chemotherapy-based	197 (65)
TBI-based	107 (35)
BMI, n (%)	
<25	111 (37)
25-30	117 (38)
>30	76 (25)
Total ATG dose, mg, median (range)	370 (130-510)
Total ATG dose, n (%)	
≤450 mg	279 (92)
>450 mg	25 (8)
ALC on day -3, K/μL, median (range)	0 (0-.6)
ALC on day -3, K/μL, n (%)	
0	200 (66)
.1	89 (29)
.2	8 (2.5)
.3	4 (1.5)
.4	2 (.5)
.6	1 (.5)

* Other hematologic malignancy: MPN, MDS/MPN overlap, non-Hodgkin lymphoma.

received a total ATG dose of ≤450 mg and 25 (8%) received a total ATG dose of >450 mg. The median total ATG dose was 360 mg (range, 130 to 510). The median weight was 107 kg (range, 90.5 to 156.2 kg) in patients who received a total ATG dose of >450 mg and 76.2 kg (range, 45.3 to 122.3 kg) in those who received a total dose of ≤450 mg. The respective median body mass index (BMI) in these 2 group of patients was 30 (range, 24.8 to 59.2) and 26.1 (range, 17.5 to 42.8). On day -3, 104 patients (34%) had an ALC >.0 K/μL (range, .1 to .6 K/μL). The median ALC on day -3 was .0 K/μL in patients receiving chemotherapy-based and TBI-based conditioning.

Association of Total ATG Dose and Treatment Outcomes

Among all patients, the cumulative incidence of acute and late-acute GVHD grade 2-4 by day 180 was 17% (95% confidence interval [CI], 13% to 21%). For patients who received a total ATG dose of >450 mg and those who received a total dose of ≤450 mg, the cumulative incidence of acute and late-acute GVHD grade II-IV at day +100 was 24% (95% CI, 10% to 42%) and 16% (95% CI, 12% to 21%), respectively (*P* = .91) (Figure 1). No patient characteristic or HCT characteristic was associated with an increased risk of GVHD in univariable analyses (data not shown).

At 1 year and 3 years post-HCT, NRM rates for all patients were 12% (95% CI, 8% to 15%) and 19% (95% CI, 15% to 24%), respectively. For patients who received a total dose of ATG >450 mg and those who received a total dose of ≤450 mg, NRM rates at 3 years were 35% (95% CI, 16% to 55%) and 18% (95% CI, 14% to 23%), respectively (*P* = .029) (Figure 2). Among all patient and HCT characteristics in univariable analyses, total ATG dose of >450 mg (hazard ratio [HR], 2.5; 95% CI, 1.2 to 5.0;

P = .03) and age (HR, 1.4 per 10 years; 95% CI, 1.1 to 1.8; *P* = .006) were associated with an increased risk of NRM (Table 2). In a multivariable analysis, increasing age (HR, 1.4; 95% CI, 1.1 to 1.8; *P* = .001) and total ATG dose >450 mg (HR, 2.9; 95% CI, 1.4 to 6.0; *P* = .01) were associated with increased risk of NRM.

At 1 year and 3 years post-HCT, DFS rates were 73% (95% CI, 68% to 78%) and 59% (95% CI, 53% to 65%), respectively. For patients receiving a total ATG dose of >450 mg and those receiving a total dose of ≤450 mg, DFS rates at 3 years were 37% (95% CI, 18% to 56%) and 61% (95% CI, 55% to 67%), respectively (*P* = .003) (Figure 3). Among all patient and HCT characteristics in univariable analyses, total ATG dose >450 (HR, 2.1; 95% CI, 1.3 to 3.5; *P* = .009), DRI (intermediate HR, 1.4; 95% CI, .6 to 3.1; high HR, 3.6; 95% CI, 1.5 to 8.6; *P* < .001), increasing age (HR, 1.2 per 10 years; 95% CI, 1.0 to 1.4; *P* = .03) and patient cytomegalovirus (CMV)-positive serostatus (HR, 1.5; 95% CI, 1.0-2.2; *P* = .03) were associated with inferior DFS (Table 3). In a multivariable analysis, receipt of a total ATG dose of >450 mg (HR, 2.0; 95% CI, 1.1 to 3.5; *P* = .03), DRI (intermediate HR, 1.2; 95% CI, .5 to 2.8; high HR, 3.2; 95% CI, 1.3 to 7.9; *P* < .001), increasing age (HR, 1.2; 95% CI, 1.0 to 1.4; *P* = .02), and patient CMV-positive serostatus (HR, 1.6; 95% CI, 1.1-2.4; *P* = .01) were associated with shorter DFS. At 1 year and 3 years post-HCT, relapse rates were 15% (95% CI, 11% to 19%) and 21% (95% CI, 17% to 26%), respectively. In univariable analyses, total ATG dose of >450 mg (HR, 1.83; 95% CI, .9 to 3.8; *P* = .14) was not associated with an increased risk of relapse (Figure 4).

At 1 year and 3 years post-HCT, OS rates were 82% (95% CI, 77% to 86%) and 65% (95% CI, 59% to 70%), respectively. For patients receiving a total ATG dose of >450 mg and those
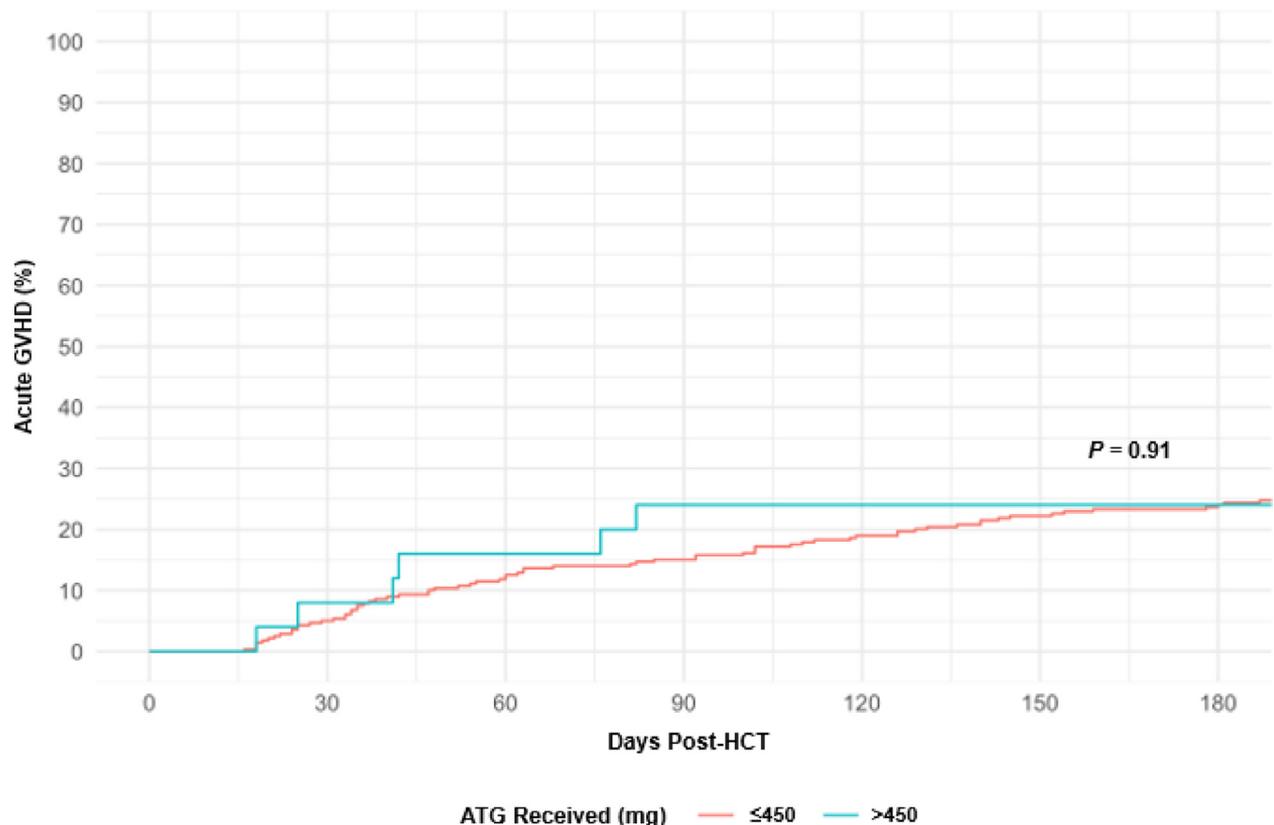

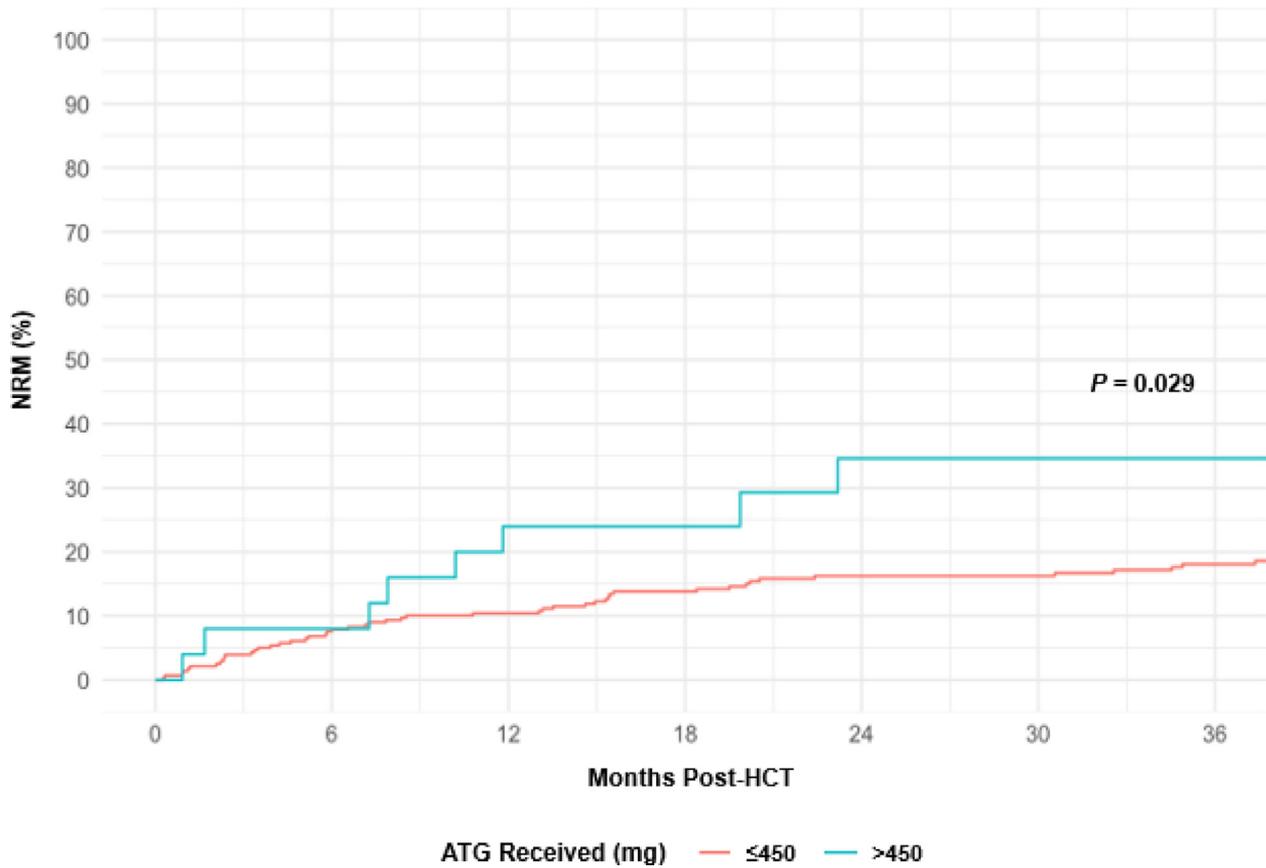**Figure 1.** Cumulative incidence of acute GVHD by total ATG dose.

Figure 2. Cumulative incidence of NRM by total ATG dose.

Table 2
Univariable Associations of Patient and HCT Characteristics with NRM

Variable		Observations	Events	HR (95% CI)	P Value
Total ATG dose					
	≤450 mg	279	52	Reference	**.03**
	>450 mg	25	9	2.5 (1.2-5.0)	
ALC on day -3					
	>0	104	15	Reference	.13
	0	200	46	1.5 (.9-2.8)	
Sex					
	Female	140	30	Reference	.81
	Male	164	31	.9 (.6-1.6)	
Disease					
	Acute leukemia	189	38	Reference	.99
	MDS	77	16	1.0 (.6-1.8)	
	Other	38	7	.9 (.4-2.1)	
Conditioning					
	Chemotherapy-based	197	46	Reference	.07
	TBI-based	107	15	.6 (.3-1.1)	
CMV serostatus					
	Negative	112	19	Reference	.15
	Positive/equivocal	192	42	1.5 (.9-2.6)	
HCT-CI					
	0	62	8	Reference	.18
	1-2	110	25	1.9 (.9-4.3)	
	≥3	132	28	1.9 (.9-4.1)	

(*continued*)

Table 2 (*Continued*)

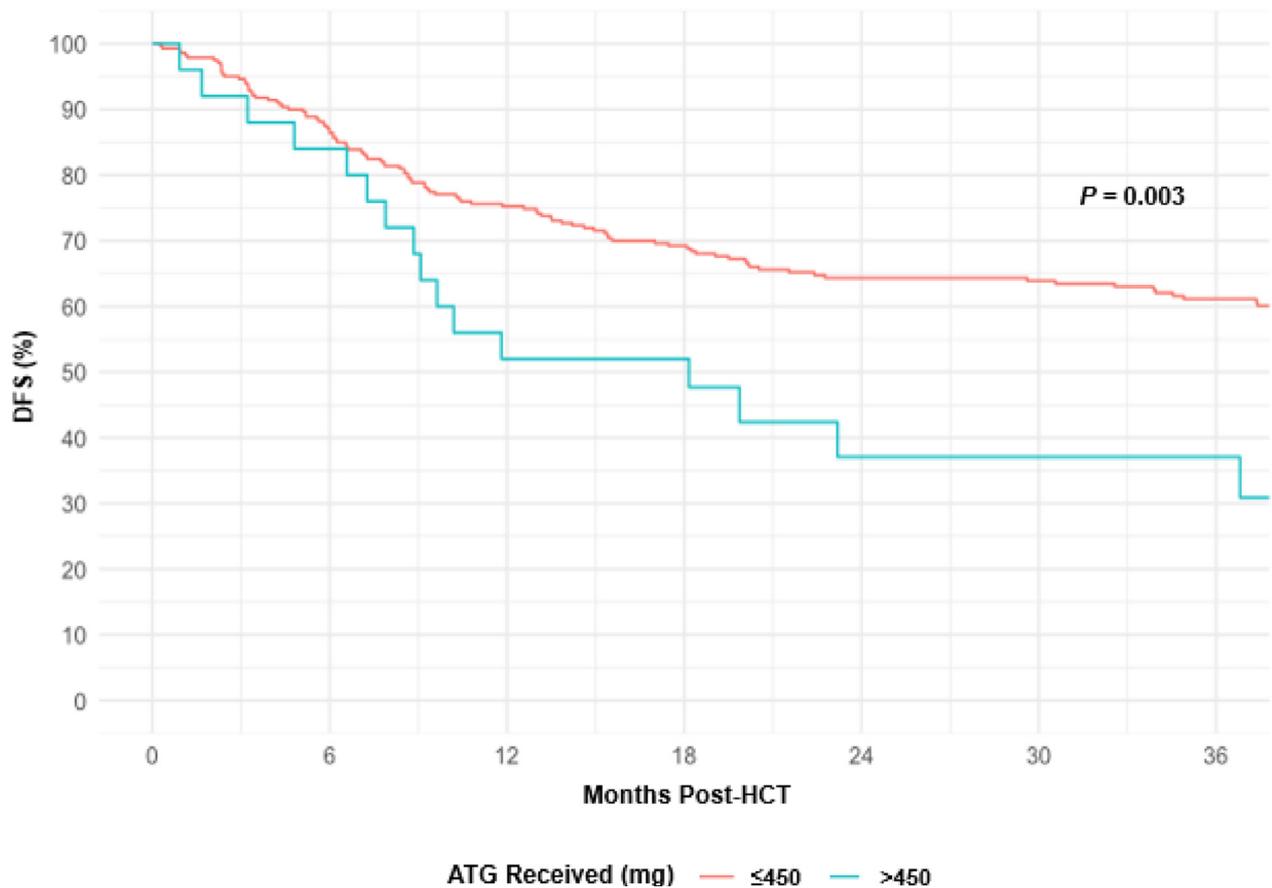| Variable		Observations	Events	HR (95% CI)	P Value
DRI					
	Low	20	2	Reference	.44
	Intermediate	237	50	2.2 (.5-9.0)	
	High	37	6	2.5 (.5-12.2)	
HLA					
	MRD	132	25	Reference	.61
	MUD	172	36	1.1 (.7-1.9)	
BMI					
	<25	111	16	Reference	.16
	25-30	117	28	1.8 (.9-3.3)	
	>30	76	28	1.6 (.8-3.1)	
Age (10 yr)		304	61	1.4 (1.1-1.8)	**.006**

Figure 3. DFS by total ATG dose.

receiving a total dose of ≤450 mg, OS rates at 3 years were 40% (95% CI, 20% to 59%) and 67% (95% CI, 61% to 72%), respectively (*P* = .001) (Figure 5). Among all patient and HCT characteristics in univariable analyses, total ATG dose >450 mg (HR, 2.4; 95% CI, 1.4 to 4.1; *P* = .004), HCT-CI (score 1-2: HR, 1.8; 95% CI, 1.0 to 3.4; score ≥3: HR, 2.2; 95% CI, 1.2 to 4.0; *P* = .02), DRI (intermediate HR, 1.9; 95% CI, .7 to 5.1; high HR, 4.9; 95% CI, 1.7 to 14.2; *P* < .001), and increasing age (HR 1.3 per 10 years; 95% CI, 1.1 to 1.5; *P* = .005) were associated with lower OS (Table 4). In a multivariable analysis stratified by HCT-CI and DRI to ensure proportional hazards, receipt of a total ATG dose of

>450 mg (HR, 2.1; 95% CI, 1.2 to 3.8; *P* = .01) and increasing age (HR, 1.2; 95% CI, 1.0 to 1.5; *P* = .02) were associated with an increased risk of all-cause death. Of the 279 patients who received a total ATG dose ≤450 mg, 93 (33%) died; of the 25 patients who received a total ATG dose >450 mg, 16 (64%) died. Table 5 summarizes outcomes and causes of death stratified by total ATG dose.

DISCUSSION

Our data show that whereas the addition of ATG to myeloablative conditioning before ex vivo CD34-selected allo-HCT

Table 3
Univariable Associations of Patient and HCT Characteristics with Inferior DFS

Variable		Observations	Events	HR (95% CI)	P value
Total ATG dose					
	≤450 mg	279	112	Reference	**.009**
	>450 mg	25	17	2.1 (1.3-3.5)	
ALC on day -3					
	>0	104	43	Reference	.95
	0	200	86	1.0 (.7-1.5)	
Sex					
	Female	140	56	Reference	.36
	Male	164	73	1.2 (.8-1.7)	
Disease					
	Acute leukemia	189	81	Reference	.86
	MDS	77	31	.9 (.6-1.4)	
	Other	38	17	1.0 (.6-1.8)	
Conditioning					
	Chemotherapy-based	197	84	Reference	.91
	TBI-based	107	45	1.0 (.7-1.5)	
CMV serostatus					
	Negative	112	40	Reference	**.03**
	Positive/equivocal	192	89	1.5 (1.0-2.2)	
HCT-CI					
	0	62	21	Reference	.12
	1-2	110	44	1.3 (.8-2.2)	
	≥3	132	64	1.6 (1.0-2.7)	
DRI					
	Low	20	6	Reference	**<.001**
	Intermediate	237	92	1.4 (.6-3.1)	
	High	37	26	3.6 (1.5-8.6)	
HLA					
	MRD	132	62	Reference	.31
	MUD	172	67	.8 (.6-1.2)	
BMI					
	<25	111	43	Reference	.54
	25-30	117	54	1.3 (.8-1.9)	
	>30	76	32	1.1 (.7-1.7)	
Age (10 y)	Not applicable	304	129	1.2 (1.0-1.4)	**.03**

Significant P values are in bold type.

mitigates the risk of primary graft rejection, the use of weight-based ATG results in overdosing in heavier patients, ultimately leading to higher NRM and lower DFS and OS [19,25]. Patients receiving a total ATG dose >450 mg also appear to have a higher incidence of relapse, though this did not meet statistical significance. The association of total ATG dose >450 mg with unfavorable outcomes remained significant even when accounting for important and validated patient and HCT characteristics, such as HCT-CI and DRI [23,24]. Given that ATG is administered based on patients' actual body weight, it is difficult to separate the effects of these 2 variables; however, BMI was not associated with inferior outcomes in our analysis, suggesting that the effect appears to be related to total ATG dose and not to weight.

Given that the median ALC on day -3 was .0 K/μL in patients receiving chemotherapy- based conditioning and those receiving TBI-based conditioning, similar overall outcomes were observed in both groups. This contrasts with a recent exploratory analysis from a randomized phase 3 study of anti-T lymphocyte globulin (ATLG) versus placebo in patients receiving myeloablative conditioned unmodified MUD allo-HCT, wherein patients receiving TBI-based conditioning with ATLG were more likely to have inferior DFS and OS compared with patients receiving chemotherapy-based conditioning with ATLG [6]. This result appeared to be a consequence of a lower ALC at the time of ATG administration in TBI-conditioned patients compared with chemotherapy-conditioned patients, again highlighting the essential interaction between ALC and ATG [6,12]. In our analysis, patients were equally lymphopenic at the time of ATG administration regardless of the conditioning regimen used. Marked lymphopenia effectively removes the metabolic sink required to clear ATG, leaving certain patients vulnerable to prolonged ATG exposure after allograft infusion [3,12]. This ATG-ALC interaction may be particularly relevant in our population given the already prolonged recovery of T cell immunity after ex vivo CD34-selected allo-HCT [25-28].
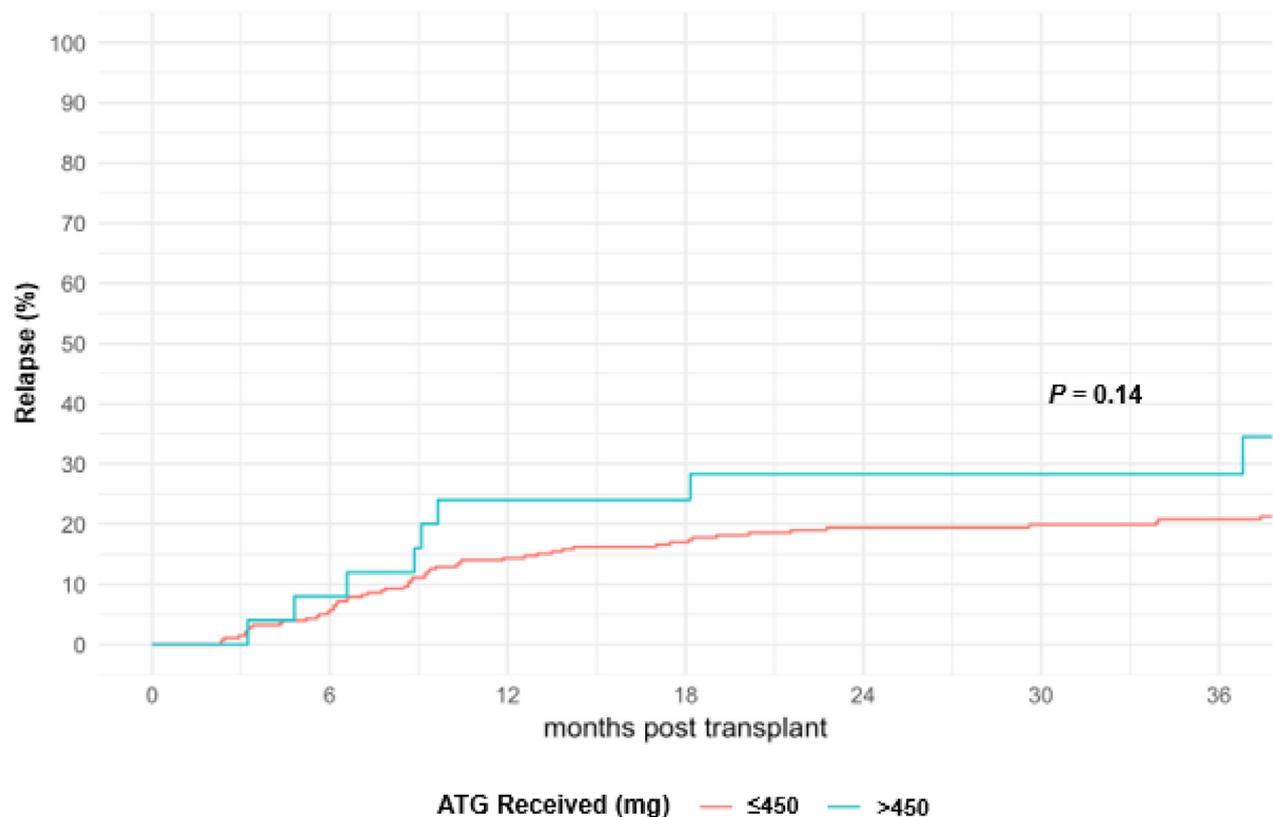
Figure 4. Cumulative incidence of relapse by total ATG dose.

It is important to recognize that the PK profile of ATG after *ex vivo* CD34-selection allo-HCT is unknown. Thus, although patients who received total ATG doses >450 mg had poorer overall outcomes, the precise dose, timing, and exposure of ATG peri-HCT needed to mitigate primary graft rejection without negatively affecting other important outcomes requires further inquiry. Interestingly, higher ATG doses did not significantly influence the incidence of acute GVHD. Given the relative rarity of GVHD after ex vivo CD34-selected allo-HCT compared with conventional allo-HCT, ATG may have a limited effect on this outcome [16,17]. We also speculate that the polyclonal nature of ATG may result in preferential reduction or preservation of specific immune effector cell subset populations that affect the risk of developing GVHD [3,29].

We have previously shown durable engraftment, low rates of opportunistic infections and GVHD, and favorable survival in patients undergoing T cell-depleted allo-HCT using a non-ATG-containing conditioning regimen of TBI, thiotepa, and fludarabine [30]. However, the use of high-dose TBI is often precluded in an increasingly elderly population because of its association with excessive regimen-related toxicity. Moreover, our results are highly relevant to an ongoing randomized, multicenter phase 3 trial of calcineurin inhibitor-free interventions for prevention of GVHD (PROGRESS II; NCT02345850), in which 1 experimental arm includes ex vivo CD34-selected allo-HCT using the ATG-containing conditioning regimens studied in our current analysis [4-6]. The systematic measurement of ATG PK levels in the context of ex vivo CD34-selected allo-HCT is crucial to determine ATG clearance in the setting of marked lymphopenia and will facilitate the development of personalized dosing that maximizes the antirejection and

anti-GVHD properties of ATG, while minimizing its adverse effects on immune reconstitution. Ultimately, this strategy may further enhance an already effective transplantation platform.

Conflict of interest statement: M.S. is an ad hoc consultant for McKinsey & Company and a consultant for Angiocrine Bioscience. V.B. is a consultant for Spectrum Pharmaceuticals and Incyte. G.L.S. receives research funding from Janssen Pharmaceuticals and Amgen. S.T.A received an honorarium in 2015 from Abbott Diagnostics. R.J.O. received royalties following licensure of the Epstein-Barr virus-specific T cell bank by Atara Biotherapeutics and has received research support and consultant fees from Atara Biotherapeutics. J.J.B. is a consultant for Avrobio, and a consulting member of the Data and Safety Monitoring Board for Magenta Therapeutics, Chimerix, and bluebird bio. M.P. receives research funding from Incyte for a clinical trial and is a consultant for Merck. M.P. serves on the ad hoc advisory boards of Incyte, Novartis, Nektar Therapeutics, and Abbvie and is on the scientific advisory boards of MolMed and Nex-Immune. M.P. is a Data and Safety Monitoring Board
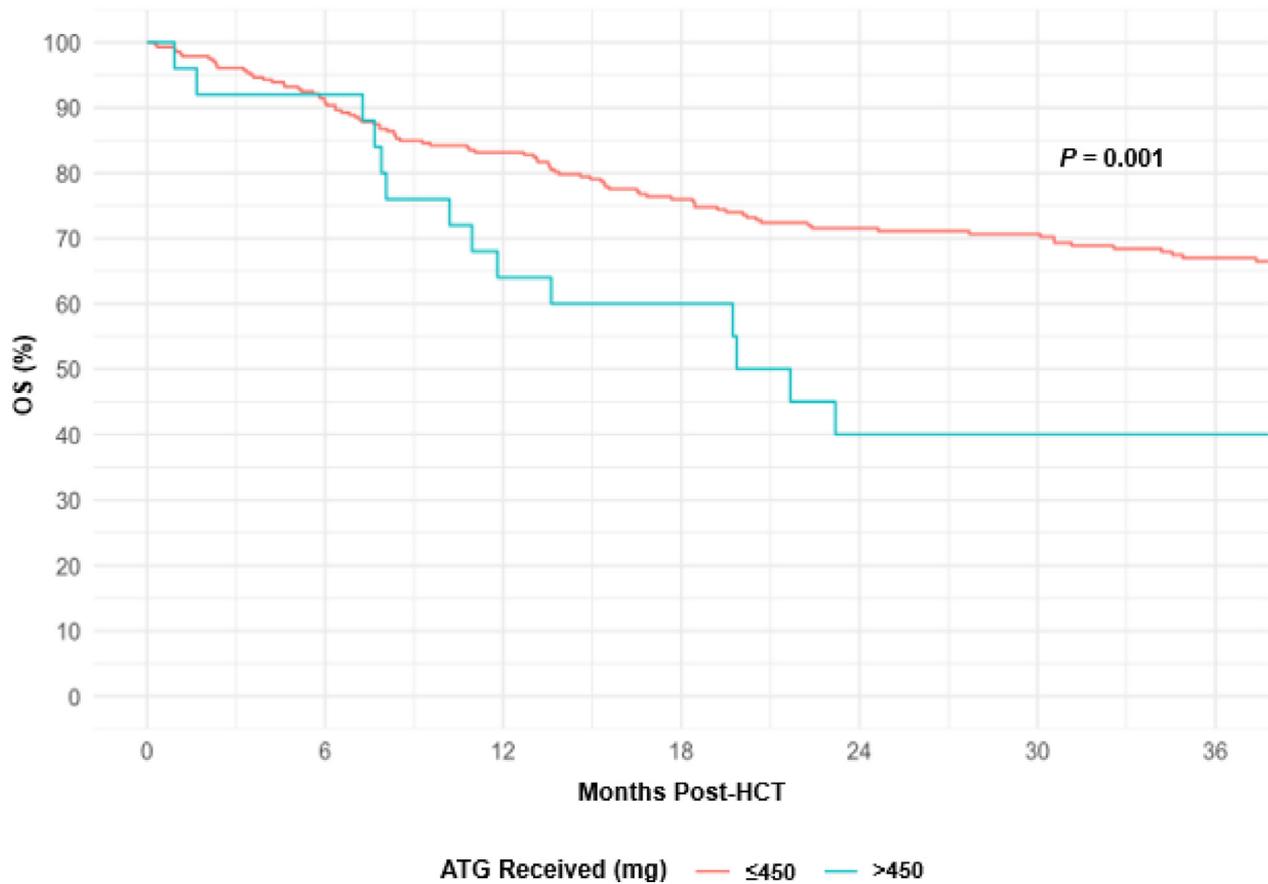
Figure 5. OS by total ATG dose.

Table 4
Univariable Associations of Patient and HCT Characteristics with OS

Variable	Observations	Events	HR (95% CI)	P value
Total ATG dose, mg				
≤450	279	93	Reference	**.004**
>450	25	16	2.4 (1.4-4.1)	
ALC on day -3				
>0	104	37	Reference	.90
0	200	72	1.2 (.7-1.2)	
Sex				
Female	140	46	Reference	.29
Male	164	63	1.23 (.84-1.8)	
Disease				
Acute leukemia	189	70	Reference	.67
MDS	77	27	.92 (.6-1.4)	
Other	38	12	.77 (.4-1.4)	
Conditioning				
Chemotherapy-based	197	74	Reference	.44
TBI-based	107	35	.85 (.6-1.3)	
CMV serostatus				
Negative	112	35	Reference	.11
Positive/equivocal	192	74	1.4 (.9-2.1)	
HCT-CI				
0	62	14	Reference	**.02**
1-2	110	39	1.8 (.99-3.4)	
≥3	132	56	2.2 (1.2-4.0)	

Table 4 (*Continued*)

Variable	Observations	Events	HR (95% CI)	P value
DRI				
Low	20	4	Reference	**<.001**
Intermediate	237	77	1.9 (.7-5.1)	
High	37	24	4.9 (1.7-14.2)	
HLA				
MRD	132	52	Reference	.52
MUD	172	57	.9 (.6-1.3)	
BMI				
<25	111	31	Reference	.12
25-30	117	47	1.5 (.9-2.5)	
>30	76	31	1.5 (.9-1.5)	
Age (10 y)	304	109	1.3 (1.1-1.5)	**.005**

Significant *P* values are in bold type.

Table 5

Patient Outcomes Stratified by ATG Dose

Variable	Total ATG Dose		P Value
	≤450 mg	>450 mg	
Grade II-IV GVHD, % at day +100	16	24	.26
NRM, %			**.03**
1-yr	10	24	
3-yr	18	35	
DFS, %			**.01**
1-yr	75	53	
3-yr	61	35	
OS, %			**.004**
1-yr	83	59	
3-yr	67	40	
Cause of death, n (%)			
Relapse	37 (40)	7 (44)	
Infection	26 (28)	4 (25)	
GVHD	14 (15)	3 (19)	
Other	16 (17)	2 (12)	

Significant *P* values are in bold type.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.02.021.

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