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Standard ATG Dosing Results in Poorer Outcomes in Overexposed Patients after *Ex vivo* CD34+ Selected Allogeneic Hematopoietic Cell Transplantation

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Abstract

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Anti-thymocyte 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 intravenously 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); 279 (92%) received a total dose of ATG ≤450 mg and 25 (8%) received a total dose >450 mg. On the first day of ATG administration (day −3), median absolute lymphocyte count was 0.0 K/μL. For patients who received a total dose of ATG >450 mg or ≤450 mg, the incidences of acute and late-acute GVHD grade 2–4 were statistically similar. At 3 years post-HCT, for patients who received a total dose of ATG >450 mg or ≤450 mg, respectively, non-relapse mortality (NRM) rates were 35% and 18%, $P = .029$, disease-free survival (DFS) rates were 37% and 61%, $P = .003$, and OS rates were 40% and 67%, $P = .001$. Among all patient and HCT characteristics in multivariable analyses, receiving a total dose of ATG >450 mg was associated with an increased risk of NRM (HR 2.9; $P = .01$), shorter DFS (HR 2.0; $P = .03$), and inferior (HR 2.1; $P = .01$). In summary, the use of weight-based ATG at a time of relative lymphopenia prior to *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.

Introduction

Many studies demonstrate that anti-thymocyte 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 multi-targeted 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 anti-cancer 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 (TCD) 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 10/10 human leukocyte antigen (HLA)-matched related (MRD) or unrelated (MUD) donors 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 intravenously 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 MPNs, MDS/MPN overlap, or non-Hodgkin lymphoma. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method. The cumulative incidence of relapse, non-relapse mortality (NRM), and GVHD were estimated using the cumulative incidence method for competing risks. Relapse and death were considered competing risks for GVHD, as well as, respectively, for NRM and relapse. 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: ROC 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 (Supplemental Material). Based on these analyses, a total ATG dose cutoff of 450 mg (corresponding to patient weights >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 follow-up among survivors was 49 months (range, 8 to 138). Neutrophil engraftment occurred in 302 (99.3%) patients, while 2 (0.7%) patients were unevaluable for engraftment because they died of infection on day 8 and day 10, respectively. Prior to allo-HCT, 295 (97%) patients received 2 infusions of ATG, and 9 (3%) received 1 infusion of ATG. Among all patients, 279 (92%) received a total ATG dose ≤450 mg and 25 (8%) received a total ATG dose >450 mg. The median total ATG dose was 360 mg (range, 130 to 510). The median weight and body mass index (BMI) of patients who received total ATG doses >450 mg or ≤450 mg, respectively, were 107 kg (range, 90.5 to 156.2) vs 76.2 kg (range, 45.3 to 122.3) and BMI 30 (range, 24.8 to 59.2) vs 26.1 (range, 17.5 to 42.8). On day –3, 104 (34%) patients had ALC >0.0 K/μL (range 0.1–0.6). Median ALC on day −3 was 0.0 K/μL for patients receiving chemo-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% CI, 13% to 21%). For patients who received a total dose of ATG >450 mg or ≤450 mg, the cumulative incidence of acute and late-acute GVHD grade 2–4 at day 100 was, respectively, 24% (95% CI, 10% to 42%) and 16% (95% CI, 12% to 21%), $P = .91$ (Figure 1). No patient characteristic or HCT characteristics was associated with an increased risk of GVHD in a univariable analysis (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 or ≤450 mg, NRM rates at 3 years were, respectively, 35% (95% CI, 16% to 55%) and 18% (95% CI, 14% to 23%), $P = .029$ (Figure 2). Among all patient and HCT characteristics in a univariable analysis, total dose of ATG >450 mg (hazard ratio [HR] 2.5; 95% CI, 1.2 to 5.0; $P = .03$) and age (HR 1.4; 95% CI, 1.1 to 1.8, per 10 years; $P = .006$) 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 dose of ATG >450 mg or ≤450 mg, DFS rates at 3 years were, respectively, 37% (95% CI, 18% to 56%) and 61% (95% CI, 55% to 67%), $P = .003$ (Figure 3). Among all patient and HCT characteristics in a univariable analysis, total ATG dose >450 (HR 2.1; 95% CI, 1.3 to 3.5; $P = .009$), DRI (intermediate HR 1.4; 95% CI, 0.6 to 3.1; and high HR 3.6; 95% CI, 1.5 to 8.6; $P < .001$), increasing age (HR 1.2; 95% CI, 1.0 to 1.4, per 10 years; $P = .03$), and patient 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, receiving a total dose of ATG >450 mg (HR 2.0; 95% CI, 1.1 to 3.5; $P = .03$), DRI (intermediate HR 1.2; 95% CI, 0.5 to 2.8; and 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; $P = .02$), patient CMV positive serostatus (HR 1.6, 95% Cl, 1.1–2.4, $P = .0.1$) 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 a univariable analysis, total dose of ATG >450 mg (HR 1.83; 95% CI, 0.9 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 dose of ATG >450 mg or ≤450 mg, OS rates at 3 years, respectively, were 40% (95% CI, 20% to 59%) and 67% (95% CI, 61% to 72%), $P = .001$ (Figure 5). Among all patient and HCT characteristics in a univariable analysis, 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; and score ≥3 HR 2.2; 95% CI, 1.2 to 4.0; $P = .02$), DRI (intermediate HR 1.9; 95% CI, 0.7 to 5.1; and high HR 4.9; 95% CI, 1.7 to 14.2; $P < .001$), and increasing age (HR 1.3; 95% CI, 1.1 to 1.5, per 10 years; $P = .005$) were associated with lower OS (Table 4). In a multivariable analysis stratified by HCT-CI and DRI to ensure proportional hazards, receiving a total dose of ATG >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 while the addition of ATG to myeloablative conditioning prior to *ex vivo* CD34-selected allo-HCT 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 given based on patients' actual body weight, it is difficult to separate the effects of these two variables. However, body mass index was not associated

with inferior outcomes in our analysis, suggesting that the effect appears to be related to total ATG dose and not weight.

Given that the median ALC on day –3 was 0.0 K/μL in patients receiving chemo- and 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-Tlymphocyte 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 when compared to patients receiving chemo-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 to chemo-conditioned patients, again highlighting the essential interaction between ALC and ATG.[6,26] 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.[25,27–29]

It is important to recognize that the PK profile of ATG after *ex vivo* CD34-selection allo-HCT is unknown. Thus, while patients who received total ATG doses >450 mg had poorer overall outcomes, the precise dose, timing, and exposure of ATG peri-HCT required to mitigate primary graft rejection without negatively affecting other important outcomes requires further inquiry. Interestingly, higher doses of ATG did not significantly influence the incidence of acute GVHD. Given the relative rarity of GVHD after *ex vivo* CD34-selected allo-HCT compared to conventional allo-HCT, ATG may have 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.[3,30]

We have previously shown durable engraftment, low rates of opportunistic infections and GVHD, and favorable survival in patients undergoing TCD allo-HCT using a non-ATG-containing conditioning regimen of TBI, thiotepa, and fludarabine.[31] 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 one experimental arm includes *ex vivo* CD34-selected allo-HCT using the ATG-containing conditioning regimens studied in our current analysis.[4,5,32] 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 anti-rejection 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Bacigalupo A, Lamparelli T, Barisione G, et al. Thymoglobulin Prevents Chronic Graft-versus-Host Disease, Chronic Lung Dysfunction, and Late Transplant-Related Mortality: Long-Term Follow-Up of a Randomized Trial in Patients Undergoing Unrelated Donor Transplantation. Biol Blood Marrow Transplant. 2006;12(5). doi:10.1016/j.bbmt.2005.12.034.
2. Finke J, Schmoor C, Bethge WA, et al. Long-term outcomes after standard graft-versus-host disease prophylaxis with or without anti-human-T-lymphocyte immunoglobulin in haemopoietic cell transplantation from matched unrelated donors: final results of a randomised controlled trial. Lancet Haematol. 2017;4(6):e293–e301. doi:10.1016/S2352-3026(17)30081-9. [PubMed: 28583289]
3. Storek J, Mohty M, Boelens JJ. Rabbit Anti-T Cell Globulin in Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2015;21(6):959–970. doi:10.1016/j.bbmt.2014.11.676. [PubMed: 25482864]
4. Kröger N, Solano C, Wolschke C, et al. Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease. N Engl J Med. 2016;374(1):43–53. doi:10.1056/NEJMoa1506002. [PubMed: 26735993]
5. Walker I, Panzarella T, Couban S, et al. Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: A randomised, controlled, open-label, phase 3, multicentre trial. Lancet Oncol. 2016;17(2):164–713. doi:10.1016/S1470-2045(15)00462-3. [PubMed: 26723083]
6. Soiffer RJ, Kim HT, McGuirk J, et al. Prospective, randomized, double-blind, phase III clinical trial of anti-T-lymphocyte globulin to assess impact on chronic graft-versus-host disease-free survival in patients undergoing HLA-matched unrelated myeloablative hematopoietic cell transplantation. J Clin Oncol. 2017;35(36):4003–4011. doi:10.1200/JCO.2017.75.8177. [PubMed: 29040031]
7. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol. 2015;33(6):540–549. doi:10.1200/JCO.2014.56.2025. [PubMed: 25154820]
8. Socie G, Schmoor C, Bethge WA, et al. Chronic graft-versus-host disease: long-term results from a randomized trial on graft-versus-host disease prophylaxis with or without anti-T-cell globulin ATG-Fresenius. Blood. 2011;117(23):6375–6382. doi:10.1182/blood-2011-01-329821. [PubMed: 21467544]
9. Soiffer RJ, LeRademacher J, Ho V, et al. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Blood. 2011;117(25):6963–6970. doi:10.1182/blood-2011-01-332007. [PubMed: 21464372]
10. Kumar A, Reljic T, Hamadani M, Mohty M, Kharfan-Dabaja MA. Antithymocyte globulin for graft-versus-host disease prophylaxis: an updated systematic review and meta-analysis. Bone Marrow Transplantation. 2018.
11. Admiraal R, van Kesteren C, Jol-van der Zijde CM, et al. Population Pharmacokinetic Modeling of Thymoglobulin® in Children Receiving Allogeneic-Hematopoietic Cell Transplantation: Towards

Improved Survival Through Individualized Dosing. Clin Pharmacokinet. 2015;54(4):435–446. doi:10.1007/s40262-014-0214-6. [PubMed: 25466602]

12. Admiraal R, Lindemans CA, Van Kesteren C, et al. Excellent T-cell reconstitution and survival depend on low ATG exposure after pediatric cord blood transplantation. Blood. 2016;128(23):2734–2741. doi:10.1182/blood-2016-06-721936. [PubMed: 27702800]
13. de Koning C, Admiraal R, Nierkens S, Boelens JJ. Immune reconstitution and outcomes after conditioning with anti-thymocyte-globulin in unrelated cord blood transplantation; the good, the bad, and the ugly. Stem Cell Investig. 2017;4:38–38. doi:10.21037/sci.2017.05.02.
14. Admiraal R, Nierkens S, de Witte MA, et al. Association between anti-thymocyte globulin exposure and survival outcomes in adult unrelated haemopoietic cell transplantation: a multicentre, retrospective, pharmacodynamic cohort analysis. Lancet Haematol. 2017;4(4):e183–e191. doi:10.1016/S2352-3026(17)30029-7. [PubMed: 28330607]
15. Kennedy VE, Chen H, Savani BN, et al. Optimizing Antithymocyte Globulin Dosing for Unrelated Donor Allogeneic Hematopoietic Cell Transplantation Based on Recipient Absolute Lymphocyte Count. Biol Blood Marrow Transplant. 2018;24(1):150–155. doi:10.1016/j.bbmt.2017.08.029. [PubMed: 28864139]
16. Pasquini MC, Devine S, Mendizabal A, et al. Comparative outcomes of donor graft CD34+ selection. J Clin Oncol. 2012;30(26):3194–3201. doi:10.1200/JCO.2012.41.7071. [PubMed: 22869882]
17. Bayraktar UD, de Lima M, Saliba RM, et al. Ex vivo T cell-depleted versus unmodified allografts in patients with acute myeloid leukemia in first complete remission. Biol Blood Marrow Transplant. 2013;19(6):898–903. doi:10.1016/j.bbmt.2013.02.018. [PubMed: 23467126]
18. Barba P, Hilden P, Devlin SM, et al. Ex Vivo CD34(+)-Selected T Cell-Depleted Peripheral Blood Stem Cell Grafts for Allogeneic Hematopoietic Stem Cell Transplantation in Acute Leukemia and Myelodysplastic Syndrome Is Associated with Low Incidence of Acute and Chronic Graft-versus-Host Disease and High Treatment Response. Biol Blood Marrow Transplant. 2017;23(3):452–458. doi:10.1016/j.bbmt.2016.12.633. [PubMed: 28017734]
19. Spitzer B, Jakubowski AA, Papadopoulos EB, et al. A Chemotherapy-Only Regimen of Busulfan, Melphalan, and Fludarabine, and Rabbit Antithymocyte Globulin Followed by Allogeneic T-Cell Depleted Hematopoietic Stem Cell Transplantations for the Treatment of Myeloid Malignancies. Biol Blood Marrow Transplant. 2017;23(12):2088–2095. doi:10.1016/j.bbmt.2017.07.004. [PubMed: 28711727]
20. Kernan NA, Bordignon C, Heller G, et al. Graft failure after T-cell-depleted human leukocyte antigen identical marrow transplants for leukemia: I. Analysis of risk factors and results of secondary transplants. Blood. 1989;74(6):2227–2236. http://www.ncbi.nlm.nih.gov/pubmed/2804361. [PubMed: 2804361]
21. Bordignon C, Keever CA, Small TN, et al. Graft failure after T-cell-depleted human leukocyte antigen identical marrow transplants for leukemia: II. In vitro analyses of host effector mechanisms. Blood. 1989.
22. Devine SM, Carter S, Soiffer RJ, et al. Low risk of chronic graft-versus-host disease and relapse associated with T cell-depleted peripheral blood stem cell transplantation for acute myelogenous leukemia in first remission: Results of the blood and marrow transplant clinical trials network prot. Biol Blood Marrow Transplant. 2011. doi:10.1016/j.bbmt.2011.02.002.
23. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014;123(23):3664–3671. doi:10.1182/blood-2014-01-552984. [PubMed: 24744269]
24. Sorror ML, Logan BR, Zhu X, et al. Prospective Validation of the Predictive Power of the Hematopoietic Cell Transplantation Comorbidity Index: A Center for International Blood and Marrow Transplant Research Study. Biol Blood Marrow Transplant. 2015;21(8):1479–1487. doi:10.1016/j.bbmt.2015.04.004.
25. Small TN, Avigan D, Dupont B, et al. Immune reconstitution following T-cell depleted bone marrow transplantation: effect of age and posttransplant graft rejection prophylaxis. BiolBlood Marrow Transplant. 1997;3(1083–8791 (Print)):65–75.

26. Admiraal R, Lindemans CA, van Kesteren C, et al. Excellent T-cell reconstitution and survival provided ATG exposure is low or absent after pediatric cord blood transplantation. Blood. 2016;128(23):2734–2742. doi:10.1182/blood-2016-06-721936. [PubMed: 27702800]
27. Small TN, Papadopoulos EB, Boulad F, et al. Comparison of immune reconstitution after unrelated and related T-cell-depleted bone marrow transplantation: effect of patient age and donor leukocyte infusions. Blood. 1999;93(2):467–480. [PubMed: 9885208]
28. Wu CJ, Chillemi A, Alyea EP, et al. Reconstitution of T-cell receptor repertoire diversity following T-cell depleted allogeneic bone marrow transplantation is related to hematopoietic chimerism. Blood. 2000;95(1):352–359. [PubMed: 10607724]
29. Keever-Taylor CA, Wagner JE, Kernan NA, et al. Comparison of immune recovery in recipients of unmanipulated vs T-cell-depleted grafts from unrelated donors in a multicenter randomized phase II-III trial (T-cell depletion trial). Bone Marrow Transplant. 2010. doi:10.1038/bmt.2009.170.
30. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus Rabbit Antithymocyte Globulin in Acquired Aplastic Anemia. N Engl J Med. 2011. doi:10.1056/NEJMoa1103975.
31. Jakubowski AA, Small TN, Young JW, et al. T cell-depleted stem-cell transplantation for adults with hematologic malignancies: Sustained engraftment of HLA-matched related donor grafts without the use of antithymocyte globulin. Blood. 2007;110(13):4552–4559. doi:10.1182/blood-2007-06-093880. [PubMed: 17717135]
32. Soiffer RJ, Kim HT, McGuirk J, et al. Prospective, randomized, double-blind, phase III clinical trial of anti-T-lymphocyte globulin to assess impact on chronic graft-versus-host disease-free survival in patients undergoing HLA-matched unrelated myeloablative hematopoietic cell transplantation. J Clin Oncol. 2017. doi:10.1200/JCO.2017.75.8177.

Highlights:

- ATG is given in a lympho-depleted state before *ex vivo* $CD34^+$ selected allo-HCT.
- Standard weight-based ATG dosing results in heavier patients receiving high total ATG doses.
- High total ATG doses results in higher NRM, and inferior DFS and OS.

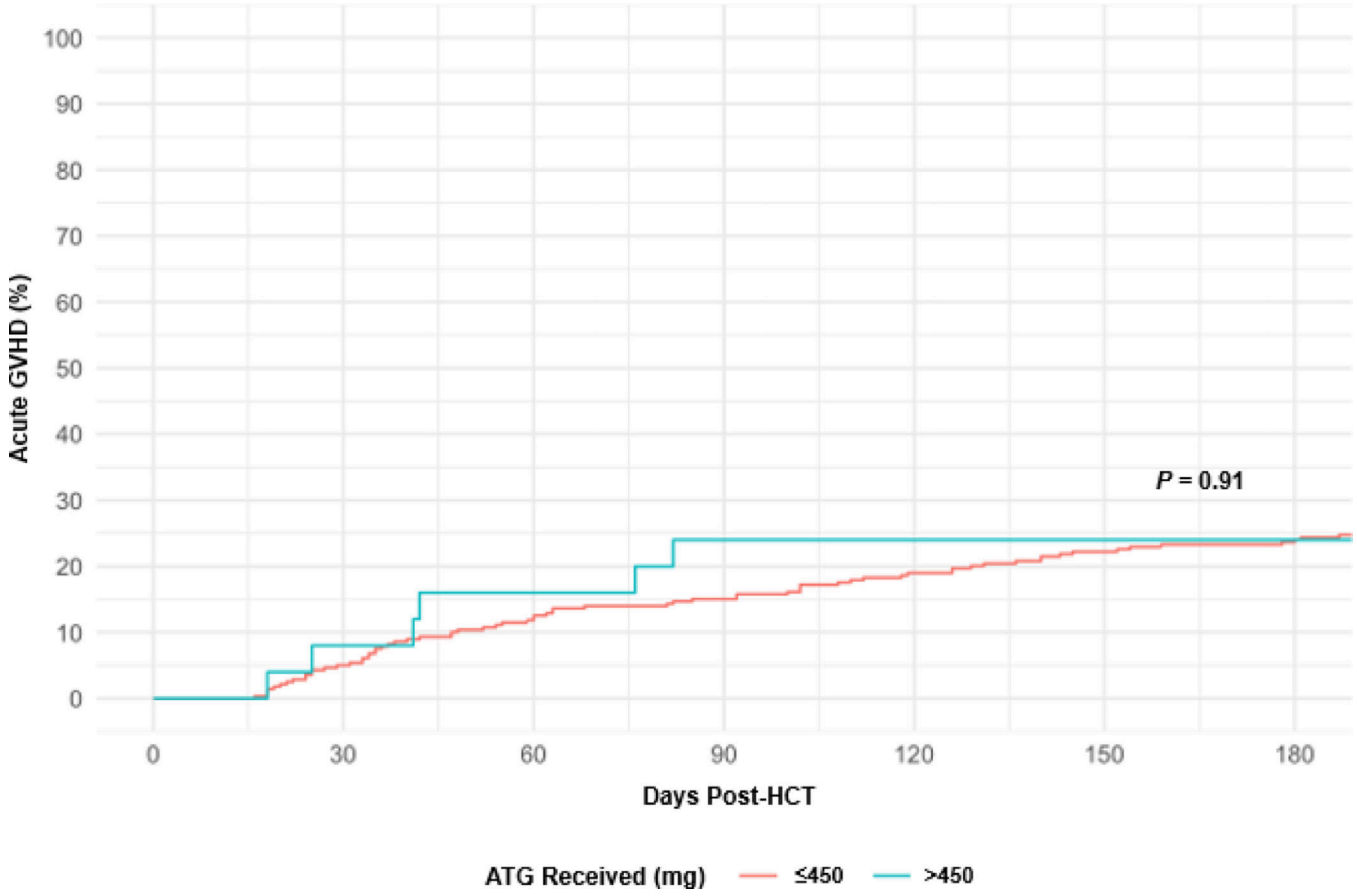

Figure 1.

Cumulative Incidence of Acute GVHD by Total ATG Dose.

ATG, anti-thymocyte globulin; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant;

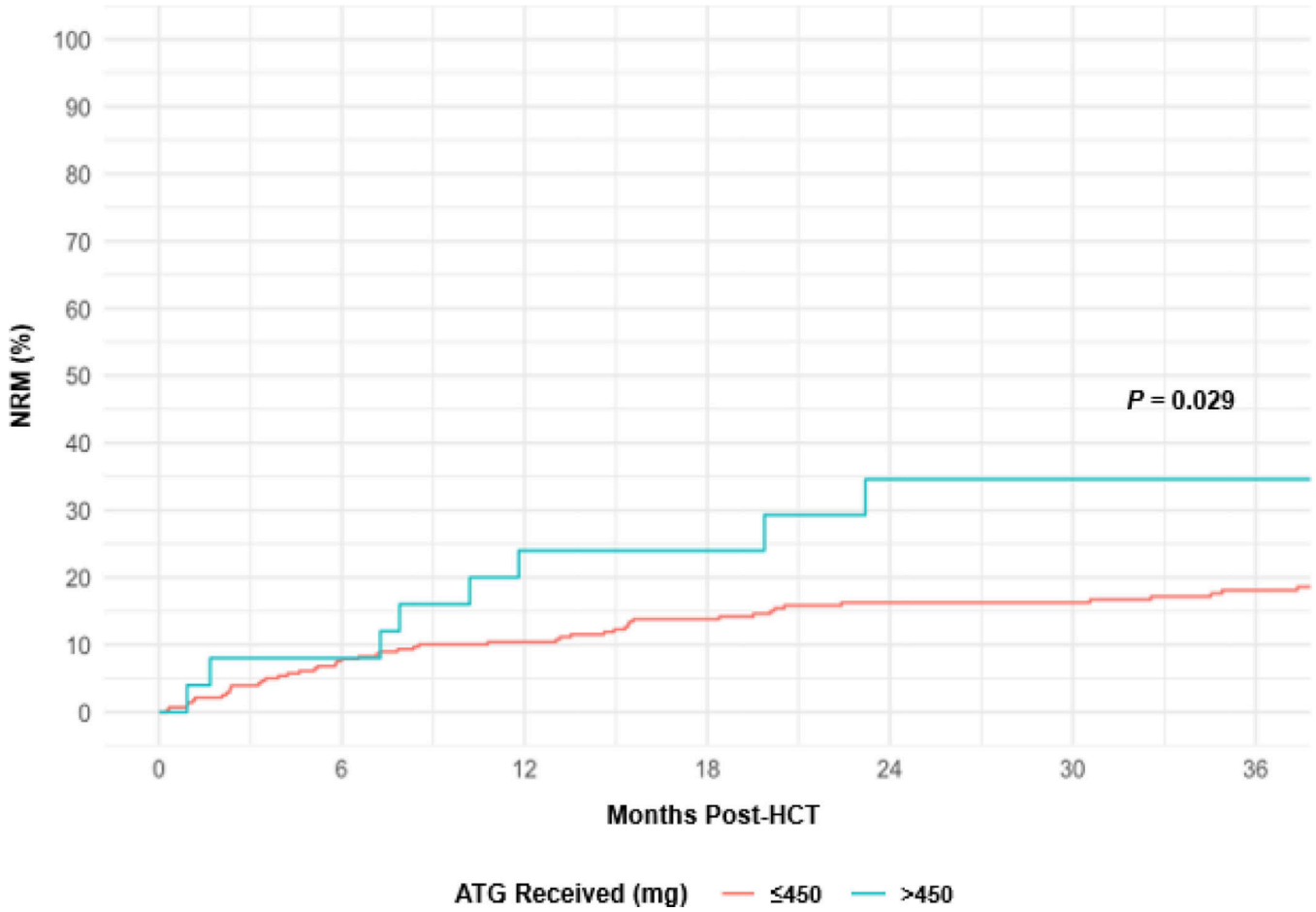

Figure 2.

Cumulative Incidence of NRM by Total ATG Dose.

ATG, anti-thymocyte globulin; HCT, hematopoietic cell transplant; NRM, non-relapse mortality.

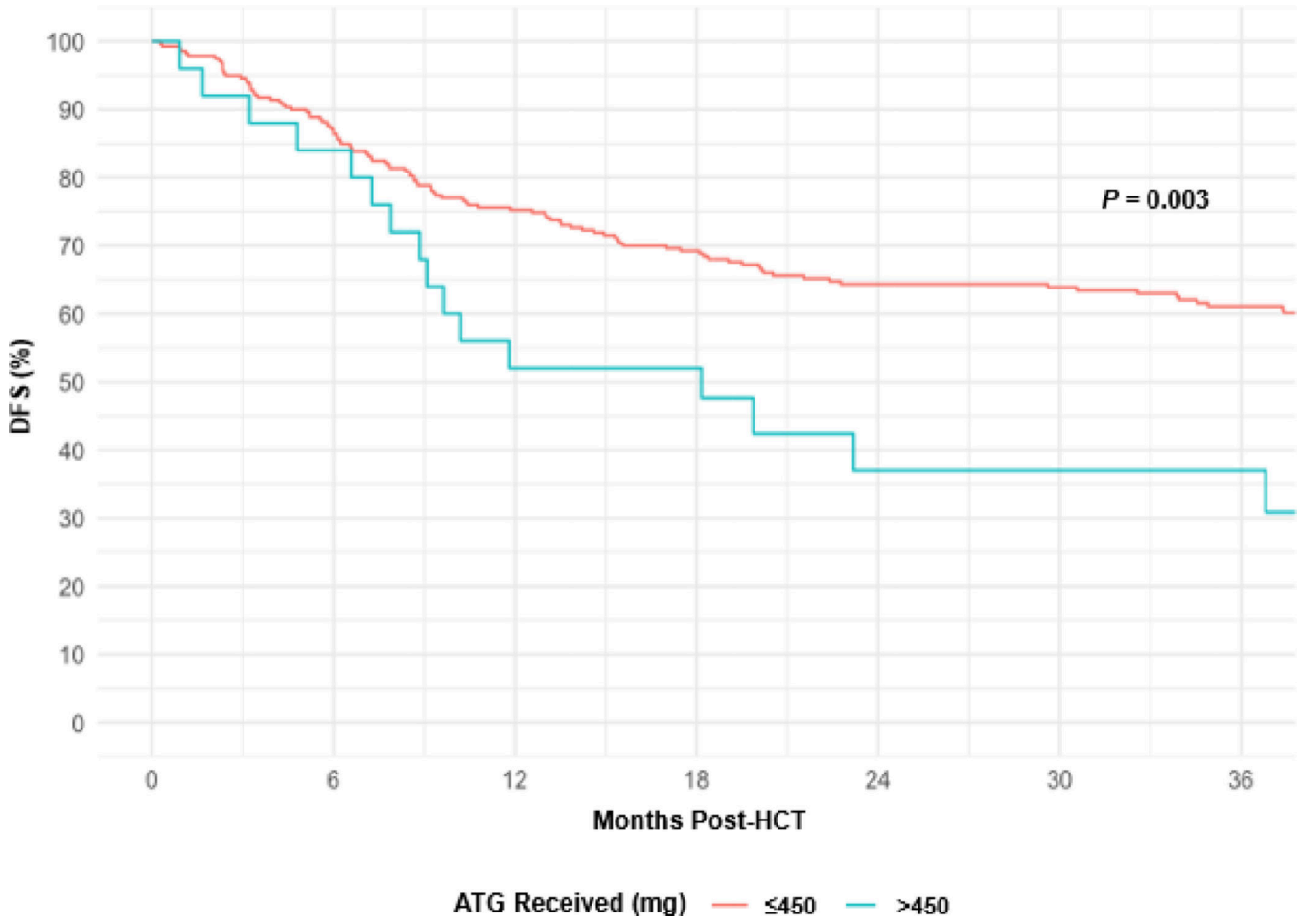

Figure 3.

DFS by Total ATG Dose.

ATG, anti-thymocyte globulin; HCT, hematopoietic cell transplant; DFS, disease-free survival.

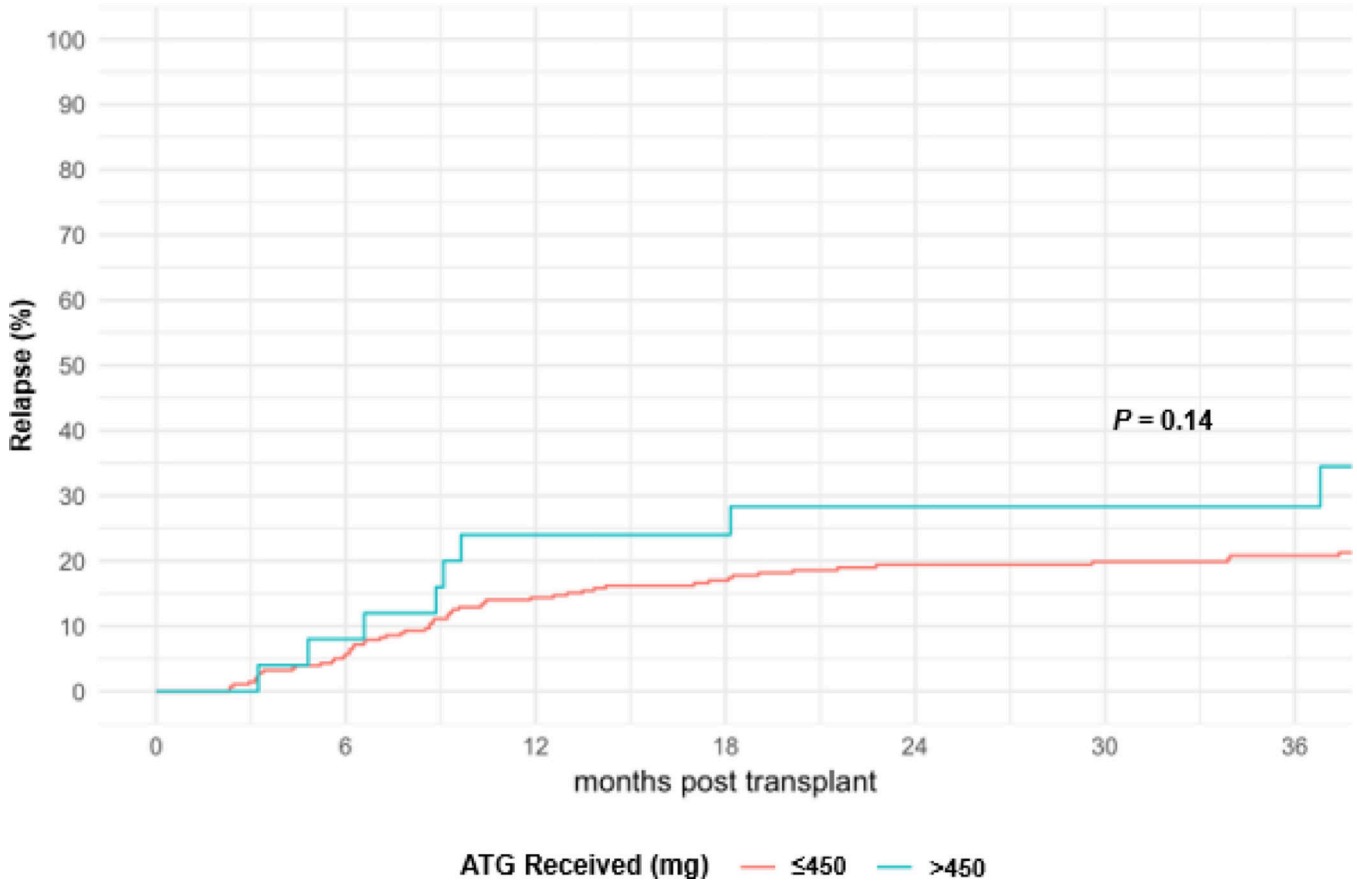

Figure 4.
Cumulative Incidence of Relapse by Total ATG Dose

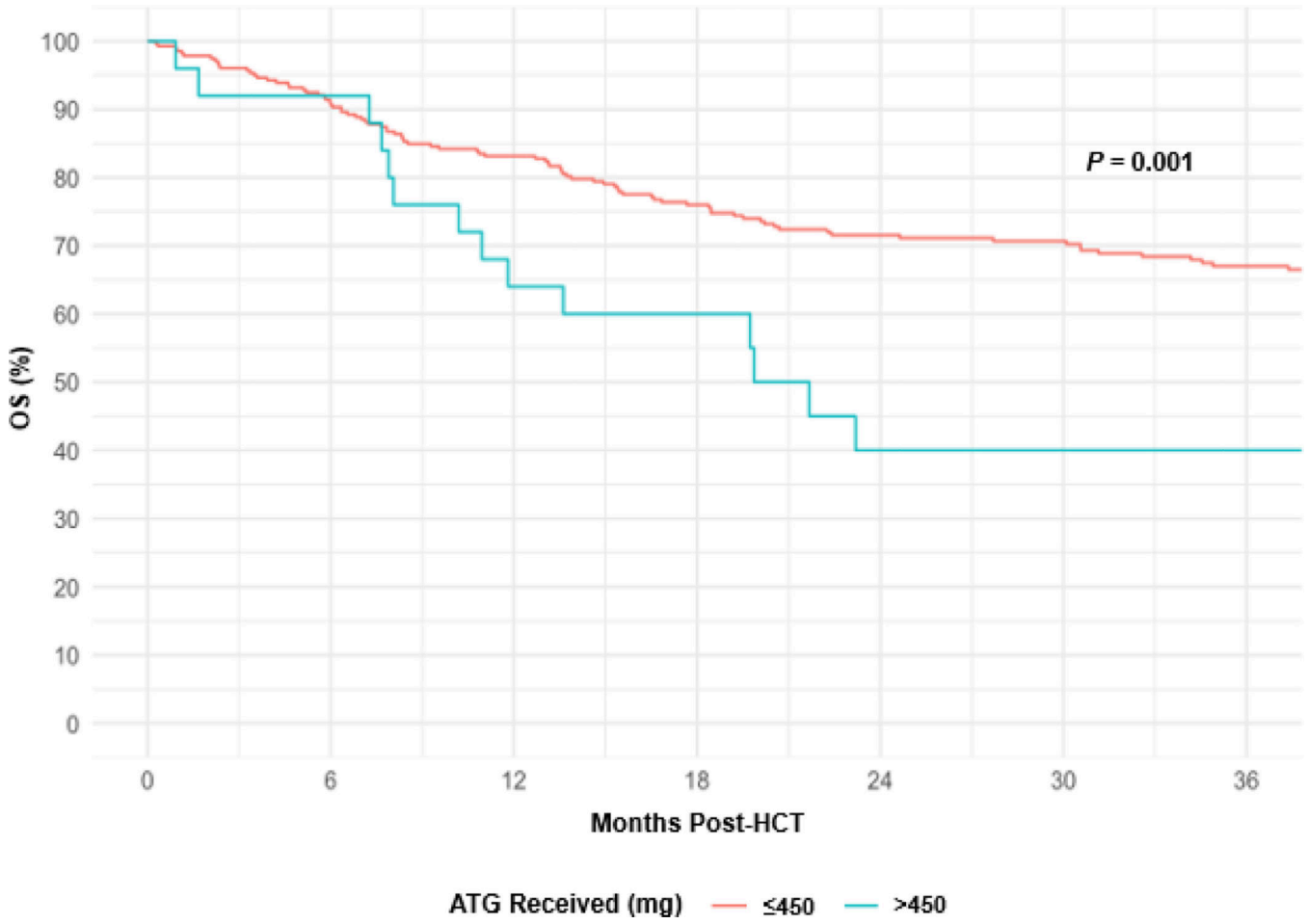

Figure 5.
OS by Total ATG Dose.
ATG, anti-thymocyte globulin; HCT, hematopoietic cell transplant; OS, overall survival.

Table 1.

Patient and Transplantation Characteristics (N = 304)

Characteristics	n (%)
Median Age (range)	56 (20–73)
Female sex	140 (46)
Disease	
Acute leukemia	189 (62)
MDS	77 (25)
Other Hematologic Malignancy	38 (13)
DRI	
Low	20 (7)
Intermediate	237 (78)
High	37 (12)
Unevaluable	10 (3)
HCT-CI	
0	62 (20)
1–2	110 (36)
>3	132 (44)
Patient CMV Serostatus	
Seropositive	192 (63)
Seronegative	112 (37)
HLA Match	
MRD	132 (43)
MUD	172 (57)
Conditioning	
Chemo-based	197 (65)
TBI-based	107 (35)
BMI	
<25	111 (37)
25–30	117 (38)
>30	76 (25)
Median Total ATG Dose, mg (range)	370 (130–510)
Total ATG Dose	
≤450 mg	279 (92)
>450 mg	25 (8)
Median ALC on Day −3, K/μL (range)	0 (0–0.6)

Characteristics	n (%)
ALC on Day −3	
0 K/μL	200 (66)
0.1 K/μL	89 (29)
0.2 K/μL	8 (2.5)
0.3 K/μL	4 (1.5)
0.4 K/μL	2 (0.5)
0.6 K/μL	1 (0.5)

Data are reported as n (%) unless otherwise noted. Other hematologic malignancy: myeloproliferative neoplasms (MPNs), MDS/MPN overlap, non-Hodgkin lymphoma. ALC, absolute lymphocyte count; ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation comorbidity index; HLA, human leukocyte antigen; MDS, myelodysplastic syndromes; MRD, matched related donor; MUD, matched unrelated donor; TBI, total-body irradiation.

Table 2.

Univariable Associations of Patient and HCT Characteristics with NRM

Variable	Group	Observations	Events	HR (95% CI)	*P* value
Total ATG Dose (mg)	<450	279	52	Reference	**0.03**
	>450	25	9	2.5 (1.2–5.0)	
ALC Day −3	>0	104	15	Reference	0.13
	0	200	46	1.5 (0.9–2.8)	
Sex	Female	140	30	Reference	0.81
	Male	164	31	0.9 (0.6–1.6)	
Disease	Acute leukemia	189	38	Reference	0.99
	MDS	77	16	1.0 (0.6–1.8)	
	Other	38	7	0.9 (0.4–2.1)	
Conditioning	Chemo-based	197	46	Reference	0.07
	TBI-based	107	15	0.6 (0.3–1.1)	
CMV Serostatus	Negative	112	19	Reference	0.15
	Positive/Equivocal	192	42	1.5 (0.9–2.6)	
HCT-CI	0	62	8	Reference	0.18
	1–2	110	25	1.9 (0.9–4.3)	
	>3	132	28	1.9 (0.9–4.1)	
DRI	Low	20	2	Reference	0.44
	Intermediate	237	50	2.2 (0.5–9.0)	
	High	37	6	2.5 (0.5–12.2)	
HLA	MRD	132	25	Reference	0.61
	MUD	172	36	1.1 (0.7–1.9)	
BMI	<25	111	16	Reference	0.16
	25–30	117	28	1.8 (0.9–3.3)	
	>30	76	28	1.6 (0.8–3.1)	
Age (10 y)		304	61	1.4 (1.1–1.8)	**0.006**

ALC, absolute lymphocyte count; ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; DRI, disease risk index; HLA, human leukocyte antigen; HCT-CI, hematopoietic cell transplantation comorbidity index; MDS, myelodysplastic syndromes; MRD, matched related donor; MUD, matched unrelated donor; TBI, total-body irradiation.

Table 3

Univariable Associations of Patient and HCT Characteristics with Inferior DFS

Variable	Group	Observations	Events	HR (95% CI)	*P* value
Total ATG Dose (mg)	<450	279	112	Reference	**0.009**
	>450	25	17	2.1 (1.3–3.5)	
ALC Day −3	>0	104	43	Reference	0.95
	0	200	86	1.0 (0.7–1.5)	
Sex	Female	140	56	Reference	0.36
	Male	164	73	1.2 (0.8–1.7)	
Disease	Acute leukemia	189	81	Reference	0.86
	MDS	77	31	0.9 (0.6–1.4)	
	Other	38	17	1.0 (0.6–1.8)	
Conditioning	Chemo-based	197	84	Reference	0.91
	TBI-based	107	45	1.0 (0.7–1.5)	
CMV Serostatus	Negative	112	40	Reference	**0.03**
	Positive/Equivocal	192	89	1.5 (1.0–2.2)	
HCT-CI	0	62	21	Reference	0.12
	1–2	110	44	1.3 (0.8–2.2)	
	>3	132	64	1.6 (1.0–2.7)	
DRI	Low	20	6	Reference	**<0.001**
	Intermediate	237	92	1.4 (0.6–3.1)	
	High	37	26	3.6 (1.5–8.6)	
HLA	MRD	132	62	Reference	0.31
	MUD	172	67	0.8 (0.6–1.2)	
BMI	<25	111	43	Reference	0.54
	25–30	117	54	1.3 (0.8–1.9)	
	>30	76	32	1.1 (0.7–1.7)	
Age (10 y)	n/a	304	129	1.2 (1.0–1.4)	**0.03**

ALC, absolute lymphocyte count; ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; DFS, disease-free survival; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation comorbidity index; HLA, human leukocyte antigen; MDS, myelodysplastic syndromes; MRD, matched related donor; MUD, matched unrelated donor; TBI, total-body irradiation.

Table 4.

Univariable Associations of Patient and HCT Characteristics with OS

Variable	Group	Observations	Events	HR (95% CI)	*P* value
Total ATG Dose (mg)	<450	279	93	Reference	**0.004**
	>450	25	16	2.4 (1.4–4.1)	
ALC Day −3	>0	104	37	Reference	0.90
	0	200	72	1.2 (0.7–1.2)	
Sex	Female	140	46	Reference	0.29
	Male	164	63	1.23 (0.84–1.8)	
Disease	Acute leukemia	189	70	Reference	0.67
	MDS	77	27	0.92 (0.6–1.4)	
	Other	38	12	0.77 (0.4–1.4)	
Conditioning	Chemo-based	197	74	Reference	0.44
	TBI-based	107	35	0.85 (0.6–1.3)	
CMV Serostatus	Negative	112	35	Reference	0.11
	Positive/Equivocal	192	74	1.4 (0.9–2.1)	
HCT-CI	0	62	14	Reference	**0.02**
	1–2	110	39	1.8 (0.99–3.4)	
	>3	132	56	2.2 (1.2–4.0)	
DRI	Low	20	4	Reference	**<0.001**
	Intermediate	237	77	1.9 (0.7–5.1)	
	High	37	24	4.9 (1.7–14.2)	
HLA	MRD	132	52	Reference	0.52
	MUD	172	57	0.9 (0.6–1.3)	
BMI	<25	111	31	Reference	0.12
	25–30	117	47	1.5 (0.9–2.5)	
	>30	76	31	1.5 (0.9–1.5)	
Age (10 y)	n/a	304	109	1.3 (1.1–1.5)	**0.005**

ALC, absolute lymphocyte count; ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation comorbidity index; HLA, human leukocyte antigen; MDS, myelodysplastic syndromes; MRD, matched related donor; MUD, matched unrelated donor; OS, overall survival; TBI, total-body irradiation.

Table 5.

Patient Outcomes Stratified by ATG Dose

Variable	Total ATG Dose (mg)		*P* value
	≤450	>450	
Grade 2–4 GVHD, %			0.26
D100	16	24	
NRM, %			**0.03**
1-year	10	24	
3-year	18	35	
DFS, %			**0.01**
1-year	75	53	
3-year	61	35	
OS, %			**0.004**
1-year	83	59	
3-year	67	40	
COD, n (%)			
Relapse	37 (40)	7 (44)	
Infection	26 (28)	4 (25)	
GVHD	14 (15)	3 (19)	
Other	16 (17)	2 (12)	

ATG, anti-thymocyte globulin; COD, cause of death; DFS, disease-free survival; GVHD, graft-versus-host disease; NRM, non-relapse mortality.