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Tacrolimus initial steady state level in post-transplant cyclophosphamide based GvHD prophylaxis regimens

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Abstract

Post-transplant cyclophosphamide (PTCy) combined with tacrolimus (TAC) as graft-versus-host disease (GvHD) prophylaxis post-hematopoietic cell transplantation (HCT) is safe and effective. Optimal serum levels of TAC in this combination remain undetermined. We hypothesized that TAC at initial steady state (TISS) of <10 ng/mL could promote optimal transplant outcomes and prevent TAC-associated toxicities. We retrospectively analyzed a consecutive case series of 210 patients who received PTCy/TAC-based prophylaxis post-HCT from 1/2013–6/2018. Patients received HCT from haploidentical (n=172) or mismatched donors (n=38), and flat dose (FD) or weight-based dose (WBD) TAC. Twenty-four-month overall survival (OS), disease free survival (DFS), and relapse rate (RR) were 61%, 56%, and 22%, respectively, in TISS <10 ng/mL cohort (n=176), and 50%, 43%, and 35%, respectively, in TISS ≥10 ng/mL cohort (n=34) (OS, P=0.71; DFS, P=0.097; RR, P=0.031). OS, DFS, RR, non-relapse mortality, acute GvHD grade II-IV, grade III-IV or chronic GvHD by TISS were similar in multivariable analysis. TISS ≥10 ng/mL conferred increased risk of viral infection (P=0.003). More patients receiving FD vs. WBD had TISS <10 ng/mL (P=0.001). Overall, TISS <10 ng/mL early post HCT conferred similar survival outcomes and lowered risk of viral infection and toxicities compared to TISS ≥10 ng/mL.

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Authorship Contributions

J.M.Y. and M.M.A. designed the study, collected and analyzed the data, and prepared the manuscript; D.Y. performed statistical analysis, interpreted data, and prepared the manuscript; M.C.C. interpreted data and prepared the manuscript; S.O., T.C., H.A., S.A., I.A., A.A., I.A., A.S., V.P., K.S., A.S., G.M., S.J.F., and R.N. interpreted data and provided critical feedback of the manuscript; and all authors reviewed the manuscript.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) remains the only potential curative treatment for many hematologic and immunologic diseases. However, prolonged time to identify appropriate matched donors and limited availability of HLA-matched donors, especially for minority and multiracial patient populations, are significant limitations for HCT(1, 2). The recent introduction of post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GvHD) prophylaxis has overcome the barrier of HLA matching, leading to increased use of mismatched related (haploidentical; Haplo) donors or unrelated donors(3, 4). PTCy-based GvHD prophylaxis is safe and promising in transplants using bone marrow (BM)(2) or peripheral blood stem cells (PBSC)(5) grafts. Multiple clinical studies (e.g. NCT03959241) are currently ongoing to assess PTCy in different HCT donor types(3, 4, 6–8).

PTCy targets alloreactive T cells while sparing stem cells and immunity to infection. PTCy may be combined with other immunosuppressants, including tacrolimus (TAC) and mycophenolate mofetil (MMF), that work through distinct mechanisms of action. TAC is a calcineurin inhibitor that inhibits T-cell activation by binding to FK506 binding intracellular proteins, and MMF is a prodrug of mycophenolic acid that prevents T- and B-cell proliferation by depleting guanosine nucleotides. The PTCy, TAC and MMF combination can effectively prevent GvHD; however, the optimal serum level of TAC in this combination has not been determined. Since TAC has a narrow therapeutic window and supratherapeutic levels are associated with numerous toxicities including renal impairment, neurotoxicity and posterior reversible encephalopathy syndrome (PRES)(9–14), it is crucial to balance TAC serum concentration to provide sufficient immunosuppression while avoiding toxicities. Target serum levels of TAC combined with methotrexate (10–20 ng/mL TAC)(15, 16) and sirolimus (5–10 ng/mL TAC)(13, 17) for HCT with matched-related or matched-unrelated donors have been established(9, 12–14), and provide guidance for serum levels in other combinations. Because PTCy inhibits alloreactive T cells and TAC broadly inhibits T-cell activation, we hypothesized that lower TAC serum levels (<10 ng/mL) could promote optimal transplant outcomes without increasing toxicity. While we did not aim to achieve a specific TAC value, we identified 10 ng/mL as a clinically relevant cut off for serum TAC levels for our analyses based on TAC use in other combinations(9, 12–14).

Weight-based dosing (WBD) has been utilized with TAC when combined with sirolimus or methotrexate(12, 17), while an initial flat dose (FD) of 1 mg TAC has been used in PTCy-based regimens(2, 18). However, TAC dosing is not standardized in PTCy-based regimens, and it is unknown whether different dosing strategies correlate with specific therapeutic TAC levels at initial steady state (TISS).

We assessed the use of TAC in a PTCy-based GvHD prophylaxis regimen in patients who received HCT. We described transplant outcomes and toxicity focusing on the effect of TISS (<10 ng/mL vs. ≥10 ng/mL) and the dosing method used to achieve TISS.

SUBJECTS AND METHODS

Patients and study design

This retrospective study was approved by the City of Hope (COH) Institutional Review Board. We retrospectively identified a consecutive case series of 210 patients who received their first allogeneic HCT with PTCy, TAC and MMF as GvHD prophylaxis at COH from January 1, 2013–June 30, 2018. Patients who received PTCy but did not initiate TAC by day +7 post-HCT or discontinued TAC before achieving TISS, as defined below, were excluded. Serum levels of TAC were assessed twice weekly from the day following initiation of TAC until discontinuation per our institution standard of practice. Peak and trough levels were not routinely measured. TISS was defined as the first serum level >48 hours post-initiation of TAC, which is ~4–5 times the TAC half-life (12 hours).

Conditioning regimen, GVHD regimen and supportive care

Conditioning regimens were selected based on patient age, comorbidities, disease type and disease status at HCT. Myeloablative (MAC) regimens included total body irradiation (TBI)-based when TBI dose was >800 cGy (e.g. fludarabine/fractionated TBI and fludarabine/cyclophosphamide/total marrow and lymph node irradiation [TMLI]) and non-TBI-based regimens (e.g. busulfan/fludarabine and busulfan/fludarabine/cyclophosphamide). Reduced intensity/non-myeloablative conditioning (RIC/NMA) included fludarabine/cyclophosphamide/TBI, fludarabine/melphalan and fludarabine/melphalan/TBI.

GvHD prophylaxis was PTCy (50 mg/kg) on day +3 and +4, TAC at WBD (0.02–0.03 mg/kg) or FD (1 mg), selected randomly per discretion of the treating physician, and MMF (15 mg/kg or 1000 mg maximum TID) both starting on day +5 post-HCT through day +90, or through day +35 in absence of severe GvHD. Patients received continuous intravenous infusion of TAC until engraftment, and then switched to equivalent oral dose in patients capable of tolerating oral administration. Granulocyte-colony stimulating factor (5 mcg/kg/day) was started on day +5 until absolute neutrophil count (ANC) reached 1500 cells/mm^3 for 3 consecutive days. All patients completed a pre-transplant workup and met creatinine clearance >60 ml/min.

All patients received supportive care and antimicrobial prophylaxis for bacterial, fungal, viral and *Pneumocystitis jiroveci* (*PJP*) infection per institutional practice. Patients were tested weekly for cytomegalovirus (CMV) infection and treated preemptively if CMV was detectable by polymerase chain reaction; 18 patients were started on CMV prophylaxis (letermovir) for CMV seropositivity per a change in our institutional practice in March 2018.

Endpoints

The primary endpoint was disease-free survival (DFS) after HCT. Secondary endpoints were acute GvHD (aGvHD), chronic GVHD (cGvHD), relapse rate (RR), non-relapse mortality (NRM), GvHD-free relapse-free survival (GRFS) and overall survival (OS).

DFS was defined as time from HCT to first observation of disease relapse or death from any cause without evidence of disease. DFS was censored at last follow-up if patients remained

alive and disease-free. aGvHD and cGvHD were graded according to established criteria(19, 20). RR and NRM were defined as incidence of relapse and death from any cause without evidence of relapse, respectively; relapse and NRM were competing risk events and were censored at last follow-up if patients were alive and free of relapse. GRFS was defined as time from transplant to first observation of the following: grade III-IV aGvHD, moderate/severe cGvHD, relapse or death, and it was censored at last follow-up if patients were alive and free of any aforementioned events. OS was defined as time from HCT to death from any cause and was censored at last follow-up if the patient was alive.

Statistical methods

Wilcoxon tests and chi-square tests were used to compare differences in baseline demographic, disease, and transplant by TISS (<10 ng/mL vs. ≥10 ng/mL). OS, DFS, and GRFS were analyzed using Kaplan-Meier curves and log-rank tests in univariate analyses. Cumulative incidence curves and Gray's tests were used for RR, NRM, aGvHD, cGvHD, and infections. Association between TAC dosing method and TISS was examined by chi-square test. Multivariable Cox proportional hazards regression models were used for OS, DFS, and GRFS when adjusting for baseline characteristics. Multivariable Fine and Gray proportional hazards regression models were used to assess RR, NRM, aGvHD, cGvHD, and infections when controlling for baseline characteristics. Stepwise selection was used to choose covariates that were significantly associated with outcomes at 0.1 level in the multivariable models. For multivariable analyses, TISS was categorized as <10 ng/mL as the reference group and ≥10 ng/mL as comparison group. P-values were 2 sided at a significance level of 0.05. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The sample size was chosen to have 80% power to detect a clinically meaningful difference (HR=2.0) in DFS by TISS using a 0.05 level two-sided log-rank test.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. Patients received HCT from haploidentical (n=172) or mismatched donors (n=38). Median age was 49 years (range, 4–73), and 122 of 210 (58.1%) patients were male. Eighty-nine of 210 (42.4%) patients received MAC, with 71 of 89 (79.8%) patients receiving a TBI-based regimen. The primary diagnosis of 125 of 210 (59.5%) patients was leukemia. The graft source for 166 of 210 (79%) patients was PBSC, while 44 of 210 (21%) patients received BM.

Overall, 176 of 210 (83.8%) had TISS <10 ng/mL and 34 of 210 (16.2%) had TISS ≥10 ng/mL. The TISS <10 ng/mL cohort included patients with subtherapeutic TISS (i.e. <5 ng/mL). Patients with TISS ≥10 ng/mL were younger than those with <10 ng/mL (median age 39 vs. 52 years, respectively; P=0.008). The majority of patients across both cohorts had leukemia (103 of 176 [58.5%] for TISS <10 ng/mL and 22 of 34 [64.7%] for TISS ≥10 ng/mL); however, there were more patients with myelodysplastic syndrome/chronic myeloid leukemia/myeloproliferative neoplasm (23.9 vs. 5.9%), but fewer patients with non-malignant diseases (8.5% vs. 14.7%) in the TISS <10 ng/mL vs. TISS ≥10 ng/mL group, respectively. The majority with TISS <10 ng/mL received PBSC grafts (150 of 176

[85.2%] patients), and 18 of 34 (52.9%) of patients with TISS ≥10 ng/mL received BM grafts (P<0.001). The majority (131 of 210 [62.4%] patients) received FD TAC, while 79 of 210 (37.6%) patients received WBD TAC. More patients with TISS <10 ng/mL received FD than WBD TAC (67% vs. 33%), whereas more patients with TISS ≥10 ng/mL received WBD than FD TAC (61.8% vs. 38.2%) (P=0.001).

Engraftment

Median time to neutrophil engraftment was 17 days (range, 12–35) and was not statistically different by TISS (at day 28: 94% in <10 ng/mL vs. 88% in ≥10 ng/mL; Gray's test P=0.24) (Supplemental Table 1). Median time to platelet engraftment was 28 days (range, 8–101) and was not statistically different by TISS (at day 42: 80% in <10 ng/mL vs 74% in ≥10 ng/mL; Gray's test p=0.27).

Relapse & NRM

Two-year RR was 24% overall (95% CI: 18%−30%). In univariate analysis (Supplemental Table 1), patients with TISS <10 ng/mL had significantly lower RR than patients with TISS ≥10 ng/mL (22% vs. 35%, P=0.031) (Figure 1A). However, the association between RR and TISS was not significant in multivariable regression models when adjusting for disease risk, graft source and conditioning regimen (Table 2). In multivariable analysis, high/very high disease risk index (28.6% vs. 16.1% or 16.4%, HR=5.47, 95% CI:1.59–18.77, P=0.014) and BM graft source were associated with increased risk of relapse (30.1% vs. 16.5%, HR=3.63, 95% CI:1.81–7.29, P<0.001). Overall cumulative incidence of NRM at 24 months (Figure 1B) was 23% (95% CI: 17%−29%) and was similar in both cohorts (23% in <10 ng/mL and 22% in ≥10 ng/mL; P=0.79).

Survival Outcomes

With median follow-up of 24 months (range: 6.0–61.7), the 2-year OS and DFS were 59% (95% CI: 51%−66%) and 54% (95% CI: 46%−61%), respectively. There was no difference in OS by TISS (61% for <10 ng/mL vs. 50% for ≥10 ng/mL, P=0.71) (Figure 1C). Patients with TISS <10 ng/mL vs. ≥10 ng/mL had a trend of higher DFS (56% vs. 43%, respectively P=0.097) (Figure 1D). However, no significant associations were found between TISS and OS or DFS in multivariable analysis (Table 3). Overall 1-year GRFS was 50% (95% CI: 43%−56%). There was no difference in GRFS by TISS (Table 3). At 12 months, GRFS was 50% (95% CI: 42%−57%) for <10 ng/mL and 51% (95% CI: 33%−67%) for ≥10 ng/mL (P=0.91) (Figure 1E). Full univariate and multivariable analyses of survival outcomes are in Supplemental Table 2 and Table 3, respectively.

GvHD

The 100-day cumulative incidence of grade II-IV aGvHD was 43% (95% CI: 37%−50%) and grade III-IV aGvHD was 15% (95% CI: 10%−20%), and were not significantly different by TISS <10 ng/mL vs. ≥10 ng/mL (45.5% vs. 32.4%; P=0.16 for grade II-IV; and 15.9% vs. 8.8%; P=0.29 for grade III-IV; Supplemental Table 3). The overall cumulative incidence of cGvHD at 24 months was 42% (95% CI: 35%−49%) and was similar by TISS (40.2% and 31.1% for <10 ng/mL and ≥10 ng/mL, respectively; P=0.21; Supplemental Table 3).

In multivariate analysis (Table 4), BM graft source was associated with lower risk of aGvHD grade II-IV than PBSC graft source (29.5% vs. 47%; HR=0.49, 95% CI: 0.25–0.97, P=0.041).

Infection

There were no significant differences in incidence of bloodstream infection (BSI) or fungal infection by TISS in univariable (Supplemental Table 4) and multivariable (Table 5) analyses. In multivariate analysis, factors associated with BSI included KPS (<80% vs. ≥80%: 50% vs. 27.3%; HR=2.44, 95% CI: 1.38–4.32, P=0.002) and HCT-CI (≥3 vs. 0–2: 40% vs. 24.8%; HR=1.86, 95% CI: 1.02–3.37, P=0.041). Variables associated with fungal infection in multivariate analysis included age ≥60 years (P=0.016), recipient being female (P=0.033), donor CMV positivity (P=0.037) and KPS <80% (P=0.01) (Table 5). Patients with TISS ≥10 ng/mL had significantly higher risk of viral infection than patients with <10 ng/mL (91.2% vs. 77.3%) in univariable (P=0.003) and multivariable analyses (P=0.014). Recipient CMV positivity and absence of letermovir prophylaxis were associated with increased risk for CMV infection (P<0.001 and P=0.019, respectively), while no variables were associated with BK infection (Supplemental Table 5).

Day 30 discontinuation

Overall, 92% of patients continued TAC on day +30 post-HCT. Patients with TISS ≥10 ng/mL had higher early discontinuation rate on day +30 than patients with <10 ng/mL (11.8% vs 7.4%, respectively) (Table 6). Reasons for TAC discontinuation included renal insufficiency (6 of 17), neurotoxicity/PRES (7 of 17), death (2 of 17) or engraftment failure (2 of 17).

Transplant-Related Morbidities

Transplant-related morbidities are summarized in Table 6. Eight of 210 (3.8%) patients required hemodialysis within 100 days of HCT, 5 patients (2.8%) with TISS <10 ng/mL and 3 patients (8.8%) with TISS ≥10 ng/mL. Twenty of 210 (9.5%) patients were admitted to the ICU within 100 days of HCT, 8.5% with TISS <10 ng/mL and 14.7% with TISS ≥10 ng/mL. Four of 210 patients (1.9%) experienced sinusoidal obstruction syndrome, 3 patients (1.7%) with TISS <10 ng/mL and 1 patient (2.9%) with TISS ≥10 ng/mL. Fifty-nine patients had hemorrhagic cystitis within 100 days of HCT (grade 1=50 patients, grade 2=9 patients). There was no significant difference in hemorrhagic cystitis comparing TISS <10 and ≥10 ng/mL groups (30.1% vs 17.6%; P=0.14).

DISCUSSION

PTCy-based platforms effectively prevent GvHD regardless of recipient-donor HLA disparity(2, 6, 21). Despite the increased use of PTCy combined with TAC, there are currently no standard dosing guidelines or therapeutic target serum levels for TAC. It is assumed that immunosuppressive levels pre-engraftment could impact T cell repertoire and recovery, which may dictate the incidence and severity of GvHD(22–29), the graft-versus-leukemia (GvL) effect and transplant outcomes. TISS represents an early adjustable

timepoint where intervention could lead to better outcomes. Thus, it is beneficial to determine optimal TISS.

When combined with methotrexate, higher early (first week) TAC level was associated with lower risk of aGvHD grade II-IV in RIC setting(22, 29), but less GvL with higher RR(29). We observed a trend of better DFS with lower RR in patients with TISS <10 ng/mL vs. ≥10 ng/mL without affecting GvHD and NRM. This trend was not upheld in multivariable analysis when adjusted for graft source, which was previously shown to be predictive of relapse risk in patients with leukemia(5), possibly due to small sample size. One reasonable explanation is that early lower levels of suppression (TISS <10 ug/mL) permitted GvL that likely contributed to lower RR. TISS was not correlated with aGvHD or cGvHD in our analysis, as noted in TAC/methotrexate-based regimen(22, 29), which is possibly due to the upfront effect of PTCy on T cells before TAC is introduced. In our analysis, PBSCs as the graft source was the only predictor of risk of aGvHD grade II-IV, which is comparable to published data(5, 7).

Butts *et al* examined their institutional practice using initial 1 mg FD TAC to achieve the target serum level of 10–15 ng/mL(18), which they concluded required at least two dose adjustments and a median of 10 days to achieve. We found that lower TISS (<10 ng/mL) was as effective with less toxicity than higher (≥10 ng/mL), and that TISS <10ng/mL did not affect engraftment. Moreover, we observed a greater likelihood of achieving TISS <10 ng/mL with FD TAC. Our observation that TISS <10 ng/mL was sufficient to promote engraftment might be due to our study population, the majority of which received PBSC grafts; higher levels of TAC might be required to achieve engraftment with BM grafts. There were some differences in graft source and dosing strategy in our cohort due to subgroups of patients being treated on clinical protocols that required specific dosing strategies and/or graft sources. Additionally, certain pediatric transplant protocols required BM grafts and WBD. However, these subgroups represent a minority in our overall study population, and the number of patients in these subgroups were not sufficient to draw meaningful conclusions. Although we focused this study on TISS, levels of TAC beyond TISS likely influence transplant outcomes, which should be examined in future studies.

Viral infection, particularly by CMV or BK, is a main cause of treatment-related mortality following HCT. In our study, patients with TISS <10 ng/mL had lower risk of viral infection overall, which was partially due to decreased infection by BK or CMV. Lower TISS may result in lower levels of T-cell suppression and decreased incidence of viral infection. Patients with lower TISS were less likely to have TAC-associated toxicities and early discontinuation.

To our knowledge, this is the largest analysis correlating TISS with outcomes for patients who received PTCy-based GvHD prophylaxis. Our study is limited by heterogeneity of patient disease and conditioning intensity, both of which contribute to infection and transplant-related toxicities and morbidities. Additionally, few patients had early TAC dosing adjustments prior to achieving TISS, which could have affected assignment of patients to TISS cohorts. Concurrent use of azoles and other medications metabolized by CYP enzymes could affect TISS and interfere with levels of TAC beyond ISS, which could

have affected our results. However, per our institution practice, patients were on micafungin during conditioning and switched to azole prophylaxis after TISS was achieved; only 2 of 210 patients were on azoles (due to prior fungal infection) concurrently with TAC at TISS assessment. Thus, it is unlikely that azole use affected our results. It is common practice for our clinicians to avoid using medications that interfere with TAC during TAC treatment and, therefore, it is unlikely that drug-drug interactions impacted this study.

We demonstrated that lower TISS (<10 ng/mL) in the PTCy platform was acceptable, led to similar outcomes when compared to TISS >10 ng/mL, and lowered risk of viral infection and TAC-related toxicities. Our results indicate that FD TAC was sufficient to achieve <10 ng/mL in our patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Competing Interests:

Conflict of Interest Disclosure

Research reported in this publication included work performed in the Biostatistics and Mathematical Modeling Core supported by the National Cancer Institutes of Health under grant number P30CA033572. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors have no relevant conflicts of interest to declare.

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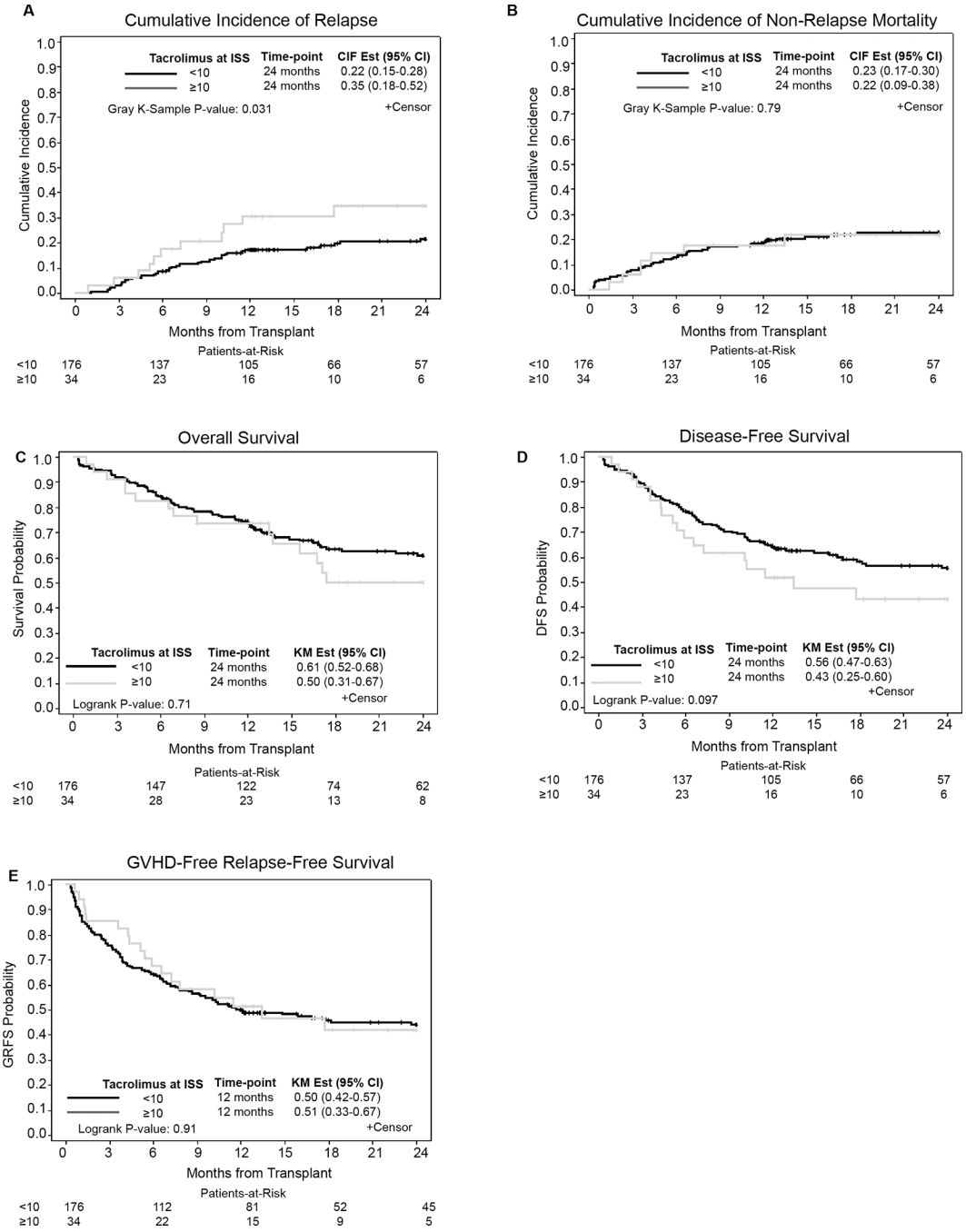

Figure 1.

Outcomes comparing <10 ng/mL vs. ≥10 ng/mL TAC at ISS cohorts. Cumulative incidence of A) relapse and B) Non-relapse mortality. Kaplan Meier curves of C) Overall survival, D) Disease-free survival and E) GVHD-Free Relapse-Free survival.

Table 1.

Patient Characteristics

	Tacrolimus level at initial steady state			
	<10 ng/mL (N=176)	**≥10 ng/mL (N=34)**	**Total (N=210)**	**p value***
Age at HSCT, years				0.008
Median	52	39	49	
Range	(4–73)	(8–65)	(4–73)	
Recipient sex, n (%)				0.071
Male	107 (60.8%)	15 (44.1%)	122 (58.1%)	
Female	69 (39.2%)	19 (55.9%)	88 (41.9%)	
Female donor to male recipient, n (%)				0.31
Yes	31 (17.6%)	3 (8.8%)	34 (16.2%)	
No	145 (82.4%)	31 (91.2%)	176 (83.8%)	
Donor age				0.68
Median	33	32	33	
Range	(10–68)	(14–49)	(10–68)	
Primary diagnosis HCT, n (%)				0.023
AML	68 (38.6%)	10 (29.4%)	78 (37.1%)	
ALL	35 (19.9%)	12 (35.3%)	47 (22.4%)	
MDS/CML/MPN	42 (23.9%)	2 (5.9%)	44 (21%)	
Lymphoma	16 (9.1%)	5 (14.7%)	21 (10%)	
Non-Malignant	15 (8.5%)	5 (14.7%)	20 (9.5%)	
DRI, n (%)				0.32
Low	29 (16.5%)	2 (5.9%)	31 (14.8%)	
Intermediate	68 (38.6%)	13 (38.2%)	81 (38.6%)	
High/Very high	64 (36.4%)	14 (41.2%)	78 (37.1%)	
Non-Malignant	15 (8.5%)	5 (14.7%)	20 (9.5%)	
Karnofsky performance status %, n (%)				0.44
80–100	146 (83%)	30 (88.2%)	176 (83.8%)	
<80	30 (17%)	4 (11.8%)	34 (16.2%)	
HCT comorbidity index, n (%)				0.78
0	54 (30.7%)	12 (35.3%)	66 (31.4%)	
1–2	49 (27.8%)	10 (29.4%)	59 (28.1%)	
≥3	73 (41.5%)	12 (35.3%)	85 (40.5%)	
Donor Type				0.051
Haploidentical	140 (79.5%)	32 (94.1%)	172 (81.9%)	
Mismatch unrelated	36 (20.5%)	2 (5.9%)	38 (18.1%)	
Graft source				<0.001
Peripheral Stem Cells	150 (85.2%)	16 (47.1%)	166 (79%)	

	Tacrolimus level at initial steady state			
	<10 ng/mL (N=176)	**≥10 ng/mL (N=34)**	**Total (N=210)**	**p value***
Bone Marrow	26 (14.8%)	18 (52.9%)	44 (21%)	
ABO blood group compatibility, n (%)				0.76
ABO compatible	116 (65.9%)	23 (67.6%)	139 (66.2%)	
Minor mismatch (donor is O)	26 (14.8%)	6 (17.6%)	32 (15.2%)	
Major mismatch (Recipient is O)	20 (11.4%)	4 (11.8%)	24 (11.4%)	
Bidirectional (None are O)	14 (8%)	1 (2.9%)	15 (7.1%)	
Donor/Recipient CMV serostatus, n (%)				0.064
D−/R−	18 (10.2%)	2 (5.9%)	20 (9.5%)	
D−/R+	43 (24.4%)	4 (11.8%)	47 (22.4%)	
D+/R−	8 (4.5%)	5 (14.7%)	13 (6.2%)	
D+/R+	107 (60.8%)	23 (67.6%)	130 (61.9%)	
Conditioning regimen, n (%)				0.55
MAC	73 (41.5%)	16 (47.1%)	89 (42.4%)	
TBI-based	60 (82.2%)	11 (68.8%)	71 (79.8%)	
Not TBI-based	13 (17.8%)	5 (31.3%)	18 (20.2%)	
RIC/NMA	103 (58.5%)	18 (52.9%)	121 (57.6%)	
GvHD prophylaxis, n (%)				1.00
PTCy / TAC / MMF	174 (98.9%)	34 (100%)	208 (99%)	
PTCy / TAC	2 (1.1%)	0 (0%)	2 (1%)	
Year of HCT, n (%)				0.10
≤2016	87 (49.4%)	22 (64.7%)	109 (51.9%)	
>2016	89 (50.6%)	12 (35.3%)	101 (48.1%)	
Letermovir				0.081
No	159 (90.3%)	34 (100%)	193 (91.9%)	
Yes	17 (9.7%)	0 (0%)	17 (8.1%)	
Tacrolimus initial dosing method, n (%)				0.001
Flat dose	118 (67%)	13 (38.2%)	131 (62.4%)	
Weight base dose	58 (33%)	21 (61.8%)	79 (37.6%)	

*P value was based on two-sample Wilcoxon test for age and donor age, Fisher's exact test or χ^2 test for other characteristics.

Table 2.

Multivariable Analysis of Engraftment, Relapse and Non-Relapse Mortality

			Neutrophil Engraftment*		Relapse†		Non-Relapse Mortality‡	
		N	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Age	<60	144	Reference	0.058	Reference	0.75	Reference	**0.005**
	≥60	66	0.72(0.52,1.01)		0.89(0.46,1.75)		3.42(1.45,8.07)	
Sex	M	122	Reference	0.57	Reference	0.054	Reference	0.096
	F	88	1.08(0.83,1.42)		0.56(0.31,1.01)		1.65(0.92,2.97)	
Female donor to male recipient	No	176	Reference	0.83	Reference	0.16	Reference	0.42
	Yes	34	0.97(0.71,1.32)		1.59(0.83,3.04)		0.71(0.31,1.63)	
Disease Risk Index	Low	31	Reference	0.26	Reference	**0.014**	Reference	0.14
	Intermediate	81	0.74(0.51,1.06)		4.01(0.99,16.29)		3.23(0.97,10.73)	
	High/Very high	78	0.84(0.58,1.22)		5.47(1.59,18.77)		3.18(0.97,10.49)	
Conditioning regimen	MAC-TBI	71	Reference	0.51	Reference	0.21	Reference	0.77
	MAC-NonTBI	18	1.01(0.61,1.68)		0.23(0.05,1.19)		0.61(0.14,2.68)	
	RIC/NMA	121	0.83(0.57,1.20)		0.75(0.39,1.44)		0.80(0.30,2.12)	
Donor type	Haploidentical	172	Reference	0.058	Reference	0.076	Reference	0.57
	Mismatched unrelated	38	1.40(0.99,1.99)		0.34(0.10,1.12)		1.23(0.60,2.49)	
ABO blood group compatibility	ABO Compatible	139	Reference	0.18	Reference	0.63	Reference	0.29
	Minor	32	1.50(1.04,2.17)		0.98(0.52,1.86)		0.31(0.09,1.05)	
	Major	24	1.05(0.75,1.49)		0.50(0.17,1.43)		0.75(0.31,1.79)	
	Bidirectional	15	1.18(0.70,1.99)		0.97(0.32,2.96)		0.94(0.31,2.87)	
Donor CMV serostatus	D+	143	Reference	0.74	Reference	0.48	Reference	0.23
	D−	67	1.05(0.79,1.40)		1.23(0.69,2.17)		0.66(0.34,1.30)	
Recipient CMV serostatus	R+	177	Reference	0.70	Reference	0.81	Reference	0.30
	R−	33	1.09(0.70,1.70)		0.90(0.38,2.13)		0.59(0.21,1.61)	
Graft source	Peripheral blood stem cells	166	Reference	**0.047**	Reference	**<0.001**	Reference	0.47
	Bone marrow	44	0.70(0.50,1.00)		3.63(1.81,7.29)		0.73(0.32,1.68)	
Karnofsky Performance Status, %	≥80	176	Reference	0.76	Reference	0.37	Reference	0.13
	<80	34	0.94(0.63,1.40)		1.41(0.66,2.99)		1.69(0.86,3.32)	
HCT-Comorbidity Index	0–2	125	Reference	**0.037**	Reference	0.85	Reference	0.16
	≥3	85	0.74(0.56,0.98)		1.05(0.62,1.81)		1.51(0.85,2.68)	
Tacrolimus initial dosing method	Flat	131	Reference	0.59	Reference	0.34	Reference	0.41

			Neutrophil Engraftment*		Relapse†		Non-Relapse Mortality‡	
		N	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
	Weight-based	79	1.08(0.82,1.43)		1.31(0.75,2.27)		1.27(0.72,2.25)	
Tacrolimus at initial steady state, ng/mL	<10	176	Reference	0.36	Reference	0.53	Reference	0.80
	≥10	34	0.83(0.56,1.23)		1.25(0.62,2.52)		1.11(0.49,2.54)	

*Adjusted for Age, Graft source, HCT-Comorbidity Index and Conditioning regimen

†Adjusted for Disease Risk Index, Graft source and Conditioning regimen

‡Adjusted for Age and Conditioning regimen

Table 3.

Multivariable Analysis of Survival Outcomes

			Overall Survival*		GvHD-Free, Relapse-Free Survival†		Disease-Free Survival‡	
		N	HR (95%CI)	Wald test P	HR (95%CI)	Wald test P	HR (95%CI)	Wald test P
Age	<60	144	Reference	**0.009**	Reference	0.34	Reference	**0.009**
	≥60	66	2.15(1.21,3.82)		1.26(0.79,2.02)		2.10(1.20,3.67)	
Sex	M	122	Reference	0.38	Reference	0.57	Reference	0.83
	F	88	1.22(0.78,1.91)		1.11(0.77,1.61)		1.05(0.69,1.59)	
Female donor to male recipient	No	176	Reference	0.35	Reference	0.88	Reference	0.88
	Yes	34	0.74(0.40,1.38)		0.97(0.60,1.55)		0.96(0.56,1.64)	
Disease Risk Index	Low	31	Reference	**0.018**	Reference	**0.002**	Reference	**<0.001**
	Intermediate	81	4.42(1.41,13.87)		4.45(1.71,11.59)		6.36(2.20,18.38)	
	High/Very high	78	4.48(1.59,12.64)		4.85(2.03,11.57)		7.83(2.98,20.58)	
Conditioning regimen	MAC-TBI	71	Reference	0.58	Reference	0.14	Reference	0.37
	MAC-NonTBI	18	0.52(0.15,1.78)		0.50(0.20,1.30)		0.44(0.14,1.38)	
	RIC/NMA	121	0.95(0.52,1.74)		1.21(0.82,1.78)		0.88(0.48,1.63)	
Donor type	Haploidentical	172	Reference	0.95	Reference	0.50	Reference	0.88
	Mismatched unrelated	38	0.98(0.54,1.77)		0.84(0.50,1.39)		0.95(0.52,1.76)	
ABO blood group compatibility	ABO Compatible	139	Reference	0.12	Reference	0.21	Reference	**0.034**
	Minor	32	0.46(0.22,0.95)		0.57(0.33,1.00)		0.47(0.25,0.89)	
	Major	24	0.56(0.26,1.21)		0.72(0.41,1.28)		0.47(0.24,0.93)	
	Bidirectional	15	0.90(0.39,2.07)		0.87(0.42,1.83)		0.81(0.36,1.83)	
Donor CMV serostatus	D+	143	Reference	0.39	Reference	0.75	Reference	0.65
	D−	67	0.80(0.49,1.33)		0.94(0.64,1.38)		0.90(0.57,1.42)	
Recipient CMV serostatus	R+	177	Reference	0.98	Reference	0.74	Reference	0.73
	R−	33	1.01(0.49,2.06)		0.91(0.51,1.60)		0.89(0.45,1.74)	
Graft source	Peripheral blood stem cells	166	Reference	0.35	Reference	0.83	Reference	**0.008**
	Bone marrow	44	1.32(0.73,2.37)		1.05(0.65,1.72)		2.12(1.22,3.70)	
Karnofsky Performance Status, %	≥80	176	Reference	0.053	Reference	0.085	Reference	**0.024**

			Overall Survival*		GvHD-Free, Relapse-Free Survival†		Disease-Free Survival‡	
		N	HR (95%CI)	Wald test P	HR (95%CI)	Wald test P	HR (95%CI)	Wald test P
	<80	34	1.70(0.99,2.91)		1.50(0.95,2.38)		1.81(1.08,3.02)	
HCT-Comorbidity Index	0–2	125	Reference	**0.035**	Reference	0.32	Reference	0.23
	≥3	85	1.61(1.03,2.51)		1.20(0.84,1.73)		1.29(0.85,1.95)	
Tacrolimus initial dosing method	Flat	131	Reference	0.30	Reference	0.82	Reference	**0.046**
	Weight-based	79	1.27(0.81,2.00)		1.05(0.72,1.53)		1.53(1.01,2.32)	
Tacrolimus at initial steady state, ng/mL	<10	176	Reference	0.32	Reference	1.00	Reference	0.29
	≥10	34	1.35(0.75,2.42)		1.00(0.62,1.63)		1.38(0.77,2.47)	

*Adjusted for Age, Disease Risk Index, Karnofsky Performance Status, HCT-Comorbidity Index and Conditioning Regimen

†Adjusted for Disease Risk Index and Conditioning Regimen

‡Adjusted for Age, Disease Risk Index, ABO blood group compatibility, Graft source, Karnofsky Performance Status and Conditioning Regimen

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Table 4.

Multivariable Analysis of GvHD

			Grade II-IV aGvHD*		Grade III-IV aGvHD†		Any cGvHD‡		Extensive cGvHD†	
		N	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Age	<60	144	Reference	0.11	Reference	0.071	Reference	0.24	Reference	0.51
	≥60	66	0.63(0.36,1.11)		0.47(0.20,1.07)		0.71(0.40,1.26)		0.79(0.39,1.59)	
Sex	M	122	Reference	0.33	Reference	0.52	Reference	0.69	Reference	0.12
	F	88	0.81(0.52,1.25)		0.79(0.37,1.65)		1.10(0.68,1.77)		1.57(0.89,2.76)	
Female donor to male recipient	No	176	Reference	0.32	Reference	0.73	Reference	**0.043**	Reference	**0.041**
	Yes	34	0.74(0.41,1.34)		0.84(0.30,2.32)		1.68(1.02,2.77)		1.81(1.02,3.21)	
Disease Risk Index	Low	31	Reference	0.50	Reference	0.50	Reference	0.81	Reference	0.38
	Intermediate	81	0.88(0.47,1.66)		1.35(0.38,4.82)		0.87(0.47,1.62)		1.64(0.72,3.72)	
	High/Very high	78	1.17(0.62,2.21)		1.93(0.56,6.64)		0.81(0.43,1.53)		1.21(0.52,2.84)	
Conditioning regimen	MAC-TBI	71	Reference	0.48	Reference	0.20	Reference	0.22	Reference	0.22
	MAC-Non- TBI	18	1.51(0.64,3.59)		0.85(0.09,8.14)		0.64(0.27,1.55)		0.72(0.28,1.85)	
	RIC/NMA	121	0.92(0.58,1.44)		1.97(0.88,4.44)		0.69(0.45,1.07)		0.64(0.38,1.06)	
Donor type	Haploidentical	172	Reference	0.22	Reference	0.43	Reference	0.41	Reference	0.64
	Mismatched unrelated	38	1.41(0.82,2.45)		1.39(0.61,3.17)		1.26(0.73,2.20)		1.17(0.61,2.23)	
ABO blood group compatibility	ABO Compatible	139	Reference	0.70	Reference	0.76	Reference	0.64	Reference	0.95
	Minor	32	1.19(0.66,2.14)		0.55(0.17,1.78)		1.38(0.76,2.49)		0.96(0.47,1.95)	
	Major	24	1.17(0.60,2.29)		1.02(0.34,3.05)		1.13(0.60,2.12)		1.08(0.49,2.36)	
	Bidirectional	15	1.50(0.75,3.00)		1.17(0.34,4.01)		1.45(0.65,3.21)		1.31(0.50,3.44)	
Donor CMV serostatus	D+	143	Reference	0.31	Reference	0.40	Reference	0.069	Reference	0.100
	D−	67	1.50(0.69,3.25)		1.38(0.65,2.92)		1.51(0.97,2.36)		1.54(0.92,2.59)	
Recipient CMV serostatus	R+	177	Reference	0.31	Reference	0.67	Reference	0.36	Reference	0.56
	R−	33	1.50(0.69,3.25)		0.76(0.21,2.72)		1.30(0.74,2.28)		1.22(0.63,2.35)	
Graft source	Peripheral blood stem cells	166	Reference	**0.041**	Reference	0.11	Reference	0.17	Reference	0.30
	Bone marrow	44	0.49(0.25,0.97)		0.36(0.10,1.27)		0.58(0.26,1.27)		0.58(0.21,1.60)	
Karnofsky Performance Status, %	≥80	176	Reference	0.68	Reference	0.37	Reference	0.61	Reference	0.47

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			Grade II-IV aGvHD*		Grade III-IV aGvHD†		Any cGvHD‡		Extensive cGvHD†	
		N	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
	<80	34	1.14(0.62,2.08)		1.48(0.63,3.47)		0.85(0.46,1.57)		0.75(0.35,1.63)	
HCT-Comorbidity Index	0–2	125	Reference	0.81	Reference	0.36	Reference	0.21	Reference	0.76
	≥3	85	0.95(0.62,1.45)		1.39(0.69,2.82)		0.75(0.48,1.17)		0.92(0.56,1.54)	
Tacrolimus initial dosing method	Flat	131	Reference	0.23	Reference	0.58	Reference	0.074	Reference	0.36
	Weight-based	79	0.76(0.48,1.19)		0.81(0.38,1.71)		0.65(0.41,1.04)		0.78(0.46,1.32)	
Tacrolimus at initial steady state, ng/mL	<10	176	Reference	0.55	Reference	0.78	Reference	0.28	Reference	0.81
	≥10	34	0.81(0.41,1.62)		0.83(0.22,3.07)		0.69(0.36,1.34)		1.08(0.56,2.12)	

*Adjusted for Donor/Recipient CMV serostatus, Graft source, and Conditioning regimen

†Adjusted for Graft source and Conditioning regimen

‡Adjusted for Female donor to male recipient and Conditioning regimen

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Table 5.

Multivariable Analysis of Infection

			Bloodstream Infection		Fungal Infection		Viral Infection*	
		N	HR (95% CI)†	P	HR (95% CI)‡	P	HR (95% CI)§	P
Age	<60	144	Reference	0.31	Reference	**0.016**	Reference	0.20
	≥60	66	1.31(0.78,2.18)		3.35(1.25,9.01)		0.76(0.50,1.15)	
Sex	M	122	Reference	0.84	Reference	**0.033**	Reference	0.10
	F	88	0.95(0.58,1.55)		3.12(1.10,8.88)		0.77(0.57,1.05)	
Female donor to male recipient	No	176	Reference	0.59	Reference	0.72	Reference	0.61
	Yes	34	1.18(0.64,2.18)		1.25(0.36,4.30)		0.90(0.61,1.34)	
Disease Risk Index	Low	31	Reference	0.80	Reference	0.71	Reference	0.15
	Intermediate	81	1.26(0.53,3.00)		2.24(0.26,19.15)		0.78(0.49,1.26)	
	High/Very high	78	1.33(0.57,3.09)		2.41(0.29,19.90)		1.12(0.71,1.76)	
Conditioning regimen	MAC-TBI	71	Reference	0.95	Reference	0.79	Reference	**<0.001**
	MAC-Non- TBI	18	1.01(0.35,2.92)		1.05(0.11,9.65)		2.22(1.22,4.05)	
	RIC/NMA	121	1.09(0.64,1.84)		1.45(0.47,4.51)		0.68(0.49,0.93)	
Donor type	Haploidentical	172	Reference	0.88	Reference	0.48	Reference	0.082
	Mismatched unrelated	38	1.05(0.57,1.90)		0.49(0.06,3.66)		0.69(0.46,1.05)	
ABO blood group compatibility	ABO Compatible	139	Reference	0.68	Reference	0.85	Reference	0.53
	Minor	32	0.92(0.45,1.88)		1.52(0.42,5.48)		0.85(0.57,1.28)	
	Major	24	1.57(0.72,3.41)		0.71(0.09,5.64)		1.34(0.78,2.29)	
	Bidirectional	15	1.03(0.46,2.33)		1.54(0.35,6.77)		1.15(0.60,2.18)	
Donor CMV serostatus	D+	143	Reference	0.88	Reference	**0.037**	Reference	0.70
	D−	67	0.96(0.57,1.62)		0.15 (0.03, 0.89)		1.22(0.45,3.31)	
Recipient CMV serostatus	R+	177	Reference	0.61	Reference	0.51	Reference	**0.012**
	R−	33	1.20(0.59,2.41)		0.54 (0.09, 3.36)		0.45(0.24,0.84)	
Graft source	Peripheral blood stem cells	166	Reference	0.49	Reference	0.88	Reference	0.28
	Bone marrow	44	1.24(0.67,2.28)		0.90(0.25,3.21)		1.26(0.83,1.90)	
Karnofsky Performance Status, %	≥80	176	Reference	**0.002**	Reference	**0.010**	Reference	0.058
	<80	34	2.44(1.38,4.32)		3.74(1.37,10.17)		1.42(0.99,2.05)	
HCT-Comorbidity Index	0–2	125	Reference	**0.041**	Reference	0.89	Reference	0.63
	≥3	85	1.86(1.02,3.37)		0.93(0.35,2.46)		0.93(0.68,1.26)	
Tacrolimus initial dosing method	Flat	131	Reference	0.78	Reference	0.28	Reference	0.062
	Weight-based	79	1.07(0.66,1.74)		1.75(0.64,4.82)		1.36(0.98,1.88)	

			Bloodstream Infection		Fungal Infection		Viral Infection*	
		N	HR (95% CI)†	P	HR (95% CI)‡	P	HR (95% CI)§	P
Tacrolimus at initial steady state, ng/mL	<10	176	Reference	0.74	Reference	0.098	Reference	**0.014**
	≥10	34	1.12(0.59,2.10)		2.40(0.85,6.78)		1.58(1.10,2.27)	

*Earliest viral infection of CMV, ADV, HHV6, BKV, or EBV

†Adjusted for Karnofsky Performance Score and HCT-Comorbidity Index

‡Adjusted for Donor/Recipient CMV serostatus

§Adjusted for Conditioning regimen and Donor/Recipient CMV serostatus

Table 6.

Transplant-related Morbidity

	Tacrolimus at Initial Steady State		
	<10 ng/mL (N=176)	**≥10 ng/mL (N=34)**	**Total (N=210)**
Continue Tacrolimus on day +30, n (%)			
No	13 (7.4%)	4 (11.8%)	17 (8.1%)
Yes	163 (92.6%)	30 (88.2%)	193 (91.9%)
Reason for Tacrolimus discontinuation, n/total n who discontinued TAC			
Renal insufficiency	4/13	2/4	6/17
Neurotoxicity/PRES	7/13	0	7/17
Engraftment failure	0	2/4	2/17
Death	1/13	1/4	2/17
Hemodialysis within day +100, n (%)			
No	171 (97.2%)	31 (91.2%)	202 (96.2%)
Yes	5 (2.8%)	3 (8.8%)	8 (3.8%)
ICU Stay, n (%)			
No	161 (91.5%)	29 (85.3%)	190 (90.5%)
Yes	15 (8.5%)	5 (14.7%)	20 (9.5%)
Sinusoidal obstruction syndrome, n (%)			
No	173 (98.3%)	33 (97.1%)	206 (98.1%)
Yes	3 (1.7%)	1 (2.9%)	4 (1.9%)
Hemorrhagic Cystitis Grade, n (%)			
No	123 (69.9%)	28 (82.4%)	151 (71.9%)
Yes	53 (30.1%)	6 (17.6%)	59 (28.1%)