Incidence, Risk Factors for and Outcomes of Transplant-Associated Thrombotic Microangiopathy

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SUMMARY

Transplant-associated thrombotic microangiopathy (TA-TMA) is a complication of allogeneic transplantation (allo-HCT). The incidence and risk factors associated with TA-TMA are not well known. A retrospective analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) was conducted including patients receiving allo-HCT between 2008 and 2016 with the primary objective of evaluating the incidence of TA-TMA. Secondary objectives included identification of risk factors associated with TA-TMA and the impact of TA-TMA on overall survival and the need for renal replacement therapy (RRT). Among 23,665 allo-HCT recipients, the 3-year cumulative incidence of TA-TMA was 3%. Variables independently associated with development increased incidence of TA-TMA included female sex, prior autologous transplant, primary disease (acute lymphoblastic leukemia and severe aplastic anemia), donor type (mismatched or unrelated donor), conditioning intensity (myeloablative), GVHD prophylaxis (sirolimus + calcineurin inhibitor), pre-transplant kidney dysfunction, and acute GVHD (time-varying effect). TA-TMA was associated with higher mortality (HR=3.1, 95%Confidence Interval [CI]=2.8-16.3) and RRT requirement (HR=7.1, 95%CI=5.7-311.6). This study provides epidemiologic data on TA-TMA and its impact on transplant outcomes. Increased awareness of the risk factors will enable providers to be vigilant of this uncommon but serious transplant complication. The results will also provide benchmarking for future study designs and comparisons.

Keywords

INTRODUCTION

Thrombotic microangiopathy belongs to the family of thrombotic endothelial disorders that also includes atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP). Transplant-associated thrombotic microangiopathy (TA-TMA) occurs when endothelial injury in the context of allogeneic hematopoietic cell transplantation (allo-HCT) causes microangiopathic hemolytic anemia and platelet consumption, resulting in microvascular thrombosis and fibrin deposition in the microcirculation.[1,2] In its most severe form, TA-TMA is associated with high mortality (60-90%)[3]; while milder cases may increase the risk of developing chronic kidney disease (CKD).[2]

The incidence of and risk factors for TA-TMA continue to be debated. The previously reported incidence of TA-TMA has ranged widely (0.5-76%), reflecting variable awareness among institutions, variable diagnostic criteria, and limited data within single institutions[4]. High-dose chemotherapy, radiation, calcineurin inhibitor (CNI) exposure, graft versus host

disease (GVHD), and infections have all been suggested as causative factors for the development of TA-TMA, but the exact pathogenesis of TA-TMA remains unknown[4].

With the increasing number of allo-HCT performed each year, there is a need to understand the epidemiology of TA-TMA and its impact on kidney function and mortality. The CIBMTR database provides an opportunity to study rare post-transplant complications. We sought to evaluate the incidence and risk factors for provider-reported TA-TMA.

METHODS

Data sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a working group of more than 500 transplant centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin (MCW) in Milwaukee, WI and the National Marrow Donor Program (NMDP)/ Be the Match in Minneapolis, MN. Participating centers are required to report all consecutive transplants and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data ensure compliance and data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The NMDP Central Institutional Review Board reviewed and approved this study.

Patients

Patients who underwent a first allo-HCT for malignant or non-malignant diseases between 2008 and 2016 were included in this analysis. Graft sources included peripheral blood, bone marrow and cord blood. Patients receiving identical twin transplants were excluded. Patients with a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) and those with non-malignant diseases with previous autologous HCT were excluded. Of note, among patients with aplastic anemia (n=1123) included in the study, 181 patients were known to have a PNH clone and were kept in the analysis. Additional exclusion criteria are detailed in Supplemental Table S1.

Definition of variables and study endpoints

In our study, we assessed the presence of TA-TMA as recorded by the individual centers as a binary outcome for "post-transplant microangiopathy-thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or similar syndrome." The CIBMTR does not stipulate a specific set of diagnostic criteria, so the presence or absence of TA-TMA was judged by the treating physicians. The intensity of conditioning regimen was defined using the consensus criteria.[5] Acute GVHD was graded using standard criteria.[6] Estimated glomerular filtration rate (eGFR) was used as a surrogate for pre-transplant kidney function. For adults, eGFR was calculated using the CKD-EPI method and for pediatric cases, it was calculated using the Bedside Schwartz method.[7–9] The primary endpoint was to evaluate cumulative incidence of provider-reported TA-TMA. Secondary endpoints included identification of risk factors associated with TA-TMA and evaluating the impact of TA-TMA on overall survival (OS) measured from time of transplant until the date of death from any

cause and estimating the risk of requiring renal replacement therapy (RRT) as identified by center as a binary response question on follow-up forms

Statistical analysis

The risk of TA-TMA was estimated using the cumulative incidence method to account for death without TA-TMA as a competing risk. Patients were censored at the time of second allo-HCT or last follow-up. Associations among baseline patient-, disease-, and transplantation-related variables and TA-TMA were evaluated using Cox proportional hazards regression model. A forward stepwise model building approach was used to identify covariates that influenced outcomes. Covariates with a $p<0.05$ were considered statistically significant. The variables considered in multivariate analysis were age, race, performance score (Karnofsky/Lansky scale), baseline kidney function, disease type, disease status, donor type, prior auto-HCT, use of anti-thymocyte globulin (ATG)/alemtuzumab, year of allo-HCT, GVHD prophylaxis, conditioning intensity, and graft type (Supplemental Table S2). Test of interaction and assumption for proportional hazards were performed in all models. To test the association between GVHD and TA-TMA, acute GVHD was tested as a time-varying covariate in the final model after adjusting for all other significant baseline covariates. For analyses of OS and need for RRT, extended Cox regression models were used to assess the impact of TA-TMA onset as a time-varying covariate. Kaplan-Meier curves were used to depict patient survival after the diagnosis of TMA. Landmark analysis at 6 months following allo-HCT was performed to compare patient survival with and without TMA.[10] All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

A total of 23,665 patients were included in the study (see Supplemental Table S1). The baseline patient-, disease- and transplant-related characteristics are shown in Table 1. The median age was 49 years (range: 1-83 years). Most of the patients were Caucasians (79%), with a male (59%) predominance and good performance status (KPS 90%, 65%). Malignant diseases comprised 88% of the study population, with acute myeloid leukemia (36%) and myelodysplastic syndrome (19%) as the most common diseases. The most common graft source used for allo-HCT was peripheral blood (60%). The majority of patients received myeloablative conditioning regimen (56%). The most common type of GVHD prophylaxis included CNI-based regimens (92%). The median time from transplant to TA-TMA was 3 months (range: 1.5–6.5 months). Median follow-up of survivors was 37 months (range 3–110 months).

Cumulative incidence of TA-TMA

The cumulative incidence of TA-TMA was 2% (95% CI=2-2%) at 1 year, and 3% (95% CI= 3-3%) at 2-years and 3-years post allo-HCT. Because these estimates were lower than those reported in several prior reports, we re-evaluated our data in several ways. First, we performed a sensitivity analysis to address potential under-reporting by examining the incidence per center and excluded centers that contributed 50 or fewer patients during the

study period and centers that reported no cases of TMA. In this scenario, the 1-year cumulative incidence increased slightly to 3%. Second, we ranked the incidence by site and noted the highest 1-year incidence in a single center was 12% (95% CI=9-15%).

Risk factors for the development of TA-TMA

On multivariable analysis, the factors that were associated with decreased risk of TA-TMA included male sex (relative to females, HR=0.70, 95%CI=0.59-0.81), use of ATG or alemtuzumab (compared to no ATG/alemtuzumab, HR=0.69, 95%CI=0.56-0.85) and reduced intensity/non-myeloablative conditioning (vs. busulfan-based myeloablative conditioning, HR=0.73, 95%CI=0.59-0.90) (Figure 1; Supplemental Table S3). In contrast, African-American race (relative to Caucasians, HR=1.46, 95%CI=1.13-1.89), a diagnosis of acute lymphoblastic leukemia (ALL) or aplastic anemia (relative to acute myeloid leukemia, HR=1.33, 95%CI=1.03-1.71 for ALL and HR=1.83, 95%CI=1.22-2.74 for aplastic anemia), poor renal function (GFR<60 relative to GFR 60, HR=1.47, 95%CI=1.08-1.99), CNI with sirolimus as GVHD prophylaxis (relative to CNI + others, HR=2.77, 95%CI=1.78-4.31), and prior auto-HCT (relative to no prior auto-HCT, HR=1.84, 95%CI=1.30-2.61) (Figure 1; Supplemental Table S3) were associated with increased risk of TA-TMA. Compared to HLA-identical sibling donor, all other donor types had increased risk for TA-TMA development; those conferring a significantly higher risk of TA-TMA were matched unrelated donor (URD) (HR=1.54, 95%CI=1.23-1.93), partially matched (7/8-matched) URD (HR=1.85, 95%CI=1.35-2.52), mismatched unrelated donor (MMUD) (<7/8-matched) (HR=4.01, 95%CI=2.02-7.95), other related donor (HR=1.51, 95%CI=1.06-2.15) and cord blood (4/6-match, HR=2.17, 95%CI=1.58-2.96) (Figure 1; Supplemental Table S3). After adjusting for all these risk factors, patients who developed acute GVHD post-transplant had a significantly higher risk of TA-TMA (grade II, HR=2.19, 95%CI=1.78-2.69; grade III-IV, HR=4.79, 95%CI=3.94-5.81) relative to those with grade I or no acute GVHD (Figure 1; Supplemental Table S3).

Impact of TA-TMA on survival and need for renal replacement therapy

In multivariate analysis, patients who developed TA-TMA had a significantly increased risk for mortality compared to those without TA-TMA considering TA-TMA as a time-dependent covariate (HR=3.09, 95%CI=2.79-16.34, p<0.001). In an unadjusted subgroup analysis, there was a higher risk of mortality in patients with TA-TMA receiving plasmapheresis relative to no plasmapheresis (HR=4.14, 95%CI=3.44-4.99, p<0.001) (Table 2). The probability of OS after diagnosis of TA-TMA was 52% at 6 months, and 42% at 1 year (Figure 2). A six-months landmark analysis showed a significantly decreased survival in patients with TA-TMA compared to those without TA-TMA (Figure 3).

Patients who developed TA-TMA had a significantly higher risk of RRT requirement compared to those without TA-TMA considering TA-TMA as a time-dependent covariate (HR=7.12, 95%CI=5.74-311.64, p<0.001) (Table 2). The median time from TA-TMA to RRT was 2.01 months (range: 0.6-2.01 months). In an unadjusted subgroup analysis, there was a significantly higher risk of RRT requirement among patients with TA-TMA receiving plasmapheresis compared to no plasmapheresis (HR=14.92, 95%CI=10.90-20.42, p<0.001) (Table 2).

Causes of Death

At last follow-up, 65% (429/661) of patients with TA-TMA and 46% (10,644/22,994) of those without TA-TMA had died (Table 3). Among TA-TMA patients, the most common cause of death was organ failure (24%), followed by primary disease (22%), infection (20%), GVHD (19%), and hemorrhage/vascular (8%). In contrast, among non-TMA patients, the most common cause of death was primary disease (45%), followed by organ failure (17%), infection (16%), and GVHD (12%), and hemorrhage/vascular (3%). The distribution of type of organ failure was similar in both groups.

DISCUSSION

In this registry-based retrospective cohort study, we identified 661 cases of provider-reported TA-TMA among 23,665 pediatric and adult allo-HCT recipients between 2008 and 2016. To our knowledge, this is the largest study to date to describe the epidemiology of this uncommon post-transplant complication. The overall provider-reported incidence of TA-TMA in the study was approximately 2-3%. We further explored the incidence of this complication over time which demonstrated no specific trend during the period of the study. Several risk factors were shown to be associated with the development of TA-TMA Patients with TA-TMA experienced substantially higher mortality with a 3-fold increased risk of death and an even higher risk of requiring renal replacement therapy of over 7-fold, compared to those without TA-TMA, confirming though rare, this is a devastating complication of allo-HCT.

It is important to contrast the incidence of *provider*-reported TA-TMA in the CIBMTR database with that of laboratory-detected TA-TMA reported in other studies. A recent study from the European Society for Blood and Marrow Transplantation (EBMT) revealed significant inter-center variability in adoption of laboratory criteria used for TA-TMA diagnosis and in agreement on schistocyte recognition and counting.[11] Among 17 centers surveyed, 41% used the International Working Group criteria[12], 41% used the overall-TMA criteria[13], and 18% used physician's decision. Due to non-standardized diagnostic criteria and multifactorial etiology of TA-TMA, as many as 64% of laboratory-detected TA-TMA cases may not be clinically recognized or reported.[14] It is likely that the under-reporting is proportionate to the severity of disease with mild TA-TMA less likely to be captured.

Given this discrepancy between laboratory-based and provider-reported TMA diagnosis, we examined other single-center studies published during the same period as our study (2008-2016). Whereas one prospective study of predominantly pediatric patients reported a 1-year cumulative incidence of 39%,[15] the remaining studies of adult patients reported a 6-month to 1-year cumulative incidence ranging from 4 to 16%.[14,16–20] These incidences are higher to what was reported to the CIBMTR, which are likely a subset of mostly more severe cases. The CIBMTR captures follow up in calendar forms and center summarizes all events that occurred in the previous reporting period. It is likely that cases of transient TA-TMA that are treated by discontinuation of CNI, for example are not clinically severe enough to be captured systematically in a retrospective matter. This is indeed a pitfall of this analysis, however the strong association between the reported TA-TMA with post-transplant outcomes strengthens the point that these provider-defined TA-TMA events were clinically

significant. Our study highlights the need for uniform consensus diagnostic criteria that are easily implementable and highly specific for TA-TMA, preferably incorporating the use of laboratory biomarkers to compliment non-specific hemolysis parameters. We recommend assessing the incidence of both *laboratory*-detected and *provider*-reported TA-TMA. We acknowledge that the former may be a surrogate for the latter and note that provider-reported TMA probably represents merely a subset of all TA-TMA which are clinically significant.

In our study, significant risk factors for TA-TMA included ALL and aplastic anemia (compared to AML), mismatched donor source (URD or CB), prior autologous transplant, CNI plus sirolimus as GVHD prophylaxis, and grade II-IV GVHD. The risk factors associated with TA-TMA in our study are consistent with the previously published studies.[13,14,16–28]. Several other risk factors were also identified in this study, including African-American race, aplastic anemia, decreased baseline GFR, and non-ATG containing conditioning. We hypothesize that patients with ALL, especially pediatric, had a higher risk of developing TA-TMA due to more frequent use of total body irradiation (TBI)-based myeloablative conditioning, which could be associated with more endothelial injury, thereby predisposing to TA-TMA. Among patients with severe aplastic anemia with a reported PNH clone, the incidence of TA-TMA was not higher than in those who received an allo-HCT without PNH (p=0.88). The use of ATG or alemtuzumab was also associated with reduced risk for TA-TMA compared to other GVHD prophylaxis regimens, as these regimens are less likely to use CNI.

The relationship between TA-TMA and acute GVHD had a gradient effect where more severe presentations of acute GVHD were associated with a higher risk for TA-TMA (HR 4.79, 95% CI=3.94-5.81 for grade III-IV vs grade I). It is hypothesized that this phenomenon may be a function of ongoing endothelial injury as the causal link. Luft et al. previously reported that both steroid-refractory GVHD and TA-TMA correlate with markers of endothelial cell dysfunction[29,30]. Wall et al. demonstrated that steroid-refractory gastrointestinal GVHD has a strong relationship with TA-TMA and proposed that complement activation serves as the mechanistic link between the two [31].

Since the majority of patients received CNI-based GVHD prophylaxis, we could not draw conclusions regarding the specific risks associated with CNI vs. no CNI. However, there was no significant difference between tacrolimus and cyclosporine-based GVHD prophylaxis as a predictor of TA-TMA. Although CNI alone did not seem to be associated with TA-TMA, we did observe a significantly increased risk of TA-TMA in patients receiving both CNI and sirolimus (HR 2.77, 95%CI=1.78-4.31). It is plausible that these two drugs act synergistically to trigger TA-TMA or perhaps sirolimus alone is sufficient to cause TA-TMA. Understanding the association between immunosuppressant drugs and TA-TMA is crucial - The Bone Marrow Transplant Clinical Trials Network Toxicity Committee consensus summary recommends CNI cessation as the first-line management option,[32] although many large cohort studies to-date reported no benefit to this approach.[14,21,27] Based on the results of the study and other recent reports,[14,19] sirolimus cessation for a patient with CNI plus sirolimus regimen is a reasonable choice but CNI cessation in patients on monotherapy should be carefully considered, given the strong association between severe GVHD and TA-TMA.

We observed a significantly higher risk of mortality and the need for RRT in patients with TA-TMA. The cause of death among TA-TMA patients was more frequently a transplant-related complication rather than disease relapse. Indeed, several prior studies have shown that TA-TMA with concurrent GVHD or infection had worse survival than TA-TMA alone. [14,19,20] Since the survival analysis was not adjusted for these time-varying complications that often occur concurrently with TA-TMA, we could not conclude whether TA-TMA onset was an independent predictor of outcomes or simply a surrogate for other complications. Similarly, the higher risk of mortality and need for RRT among the patients with TA-TMA receiving (vs. not receiving) plasmapheresis was likely reflective of providers' bias in using plasmapheresis in more severe cases of TA-TMA rather than milder cases. In addition, based on published reports, we recognize that plasmapheresis is an ineffective treatment for TA-TMA. [32,33] The study was also limited by not capturing information on other novel potential treatment modalities such as complement blockade, anti-VWF or anti-endothelial targeting.

While the study confirms that developing TA-TMA following allo-HCT carries a high risk of complications, OS appears to be better than historic cohorts. A comprehensive systematic review published in 2004 by George *et al.* reported that patients with TA-TMA had median cumulative mortality of 75%, with 82% of deaths occurring within 3 months of diagnosis. [3] The median OS in our study was 6 months and the cumulative mortality was 35% at 3 months and 60% during longer follow-up. This result is consistent with several recently published single-center cohort studies; the reasons are unclear, particularly given the lack of substantive improvements in supportive care for this condition and the lack of improvement in survival over time (data not shown). However, given the strong link between TA-TMA and severe GVHD, it is plausible that the improvement in OS in the TA-TMA cohort is largely related to the advances in treatment of GVHD and allied supportive care in the current era. [34]

In conclusion, this study describes the epidemiology of TA-TMA, risk factors, the impact of TA-TMA and its treatment on subsequent HCT outcomes. As an observational cohort for TA-TMA, these results may be useful for benchmarking for future comparative studies and clinical trial designs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LIST OF ABBREVIATIONS

TA-TMA	transplant-associated thrombotic microangiopathy
Allo-HCT	Allogeneic hematopoietic cell transplantation
TED	Transplant Essential Data
CRF	Comprehensive Report Form
HCT-CI	HCT comorbidity index
Cy	cyclophosphamide
GFR	glomerular filtration rate
GVHD	graft-versus-host disease
URD	unrelated donor

CNI	calcineurin inhibitor
TAC	tacrolimus
CSA	cyclosporine
ATG	anti-thymocyte globulin
CB	cord blood
OS	overall survival
PFS	progression-free survival
HR	hazard ratio
CI	confidence interval
TA-TMA	transplant associated thrombotic microangiopathy
RRT	renal replacement therapy
KPS	Karnofsky performance status

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Multivariable Cox regression model for TMA	HR	95% CI	Pointwise p-value
Gender (female is reference)			
Male	0.70	(0.59, 0.81)	<0.001
Race (Caucasian is reference)			
African American	1.46	(1.13, 1.89)	0.004
Other race	1.04	(0.77, 1.42)	0.78
Unknown	0.93	(0.31, 2.76)	0.89
ATG/alemtuzumab use (None used is reference)			
ATG +/- alemtuzumab	0.69	(0.56, 0.85)	<0.001
Alemtuzumab alone	1.14	(0.77, 1.70)	0.52
Conditioning regimen (MAC Bu-based is reference)			
Myeloablative TBI	1.12	(0.88, 1.43)	0.34
Other myeloablative	0.92	(0.56, 1.50)	0.74
RIC/NMA	0.73	(0.59, 0.90)	0.003
Disease (AML is reference)			
ALL	1.33	(1.03, 1.71)	0.03
CLL	0.92	(0.54, 1.57)	0.77
CML	0.69	(0.39, 1.21)	0.20
MDS	1.18	(0.93, 1.50)	0.16
MPN	1.35	(0.90, 2.02)	0.15
Other acute leukemia	0.81	(0.36, 1.84)	0.62
Lymphoma	1.16	(0.84, 1.58)	0.37
Plasma cell disorder	1.71	(0.96, 3.05)	0.07
Immune disorder	1.20	(0.73, 1.98)	0.48
Inborn error of metabolism	1.32	(0.53, 3.34)	0.55
Aplastic anemia	1.83	(1.22, 2.74)	0.003
Hemoglobinopathy	0.52	(0.22, 1.23)	0.14
Inherited BM failure syndrome	1.77	(0.92, 3.40)	0.09
Donor type (HLA-identical sibling is reference)			
Other relative	1.51	(1.06, 2.15)	0.03
Matched URD (8/8)	1.54	(1.23, 1.93)	<0.001
Partially matched URD (7/8)	1.85	(1.35, 2.52)	<0.001
Mismatched URD (<7/8)	4.01	(2.02, 7.95)	<0.001
URD, HLA match unknown	1.79	(0.96, 3.33)	0.07
CB 6/6	1.67	(0.99, 2.82)	0.06
CB 5/6	1.31	(0.92, 1.87)	0.14
CB <5/6	2.17	(1.58, 2.96)	<0.001
CB, HLA match unknown	1.16	(0.67, 2.01)	0.59
Kidney function (GFR>=60 is reference)			
GFR <60	1.47	(1.08, 1.99)	0.02
GFR unknown	0.79	(0.29, 2.11)	0.63
GVHD prophylaxis (CNI + post-Cy is reference)			
CNI + siro	2.77	(1.78, 4.31)	<0.001
Siro (no CNI or post-Cy)	1.01	(0.35, 2.95)	0.98
Csa (no Tac, Siro or post-Cy)	1.06	(0.68, 1.65)	0.80
Tac (no Csa, Siro or post-Cy)	0.88	(0.58, 1.34)	0.56
Other prophylaxis strategy	1.10	(0.67, 1.81)	0.70
Prior autologous transplant (No prior auto is reference)			
Prior auto-HCT	1.84	(1.30, 2.61)	0.001
Unknown	1.30	(0.50, 3.34)	0.59
Acute GVHD* (Grade 0-1 is reference)			
Grade 2	2.19	(1.78, 2.69)	<0.001
Grade 3-4	4.79	(3.94, 5.81)	<0.001

*Time-dependent covariate adjusted for all above variables

Figure 1.
Forest plot of multivariate model for TA-TMA

Figure 2.
Overall Survival after TA-TMA diagnosis

Figure 3.
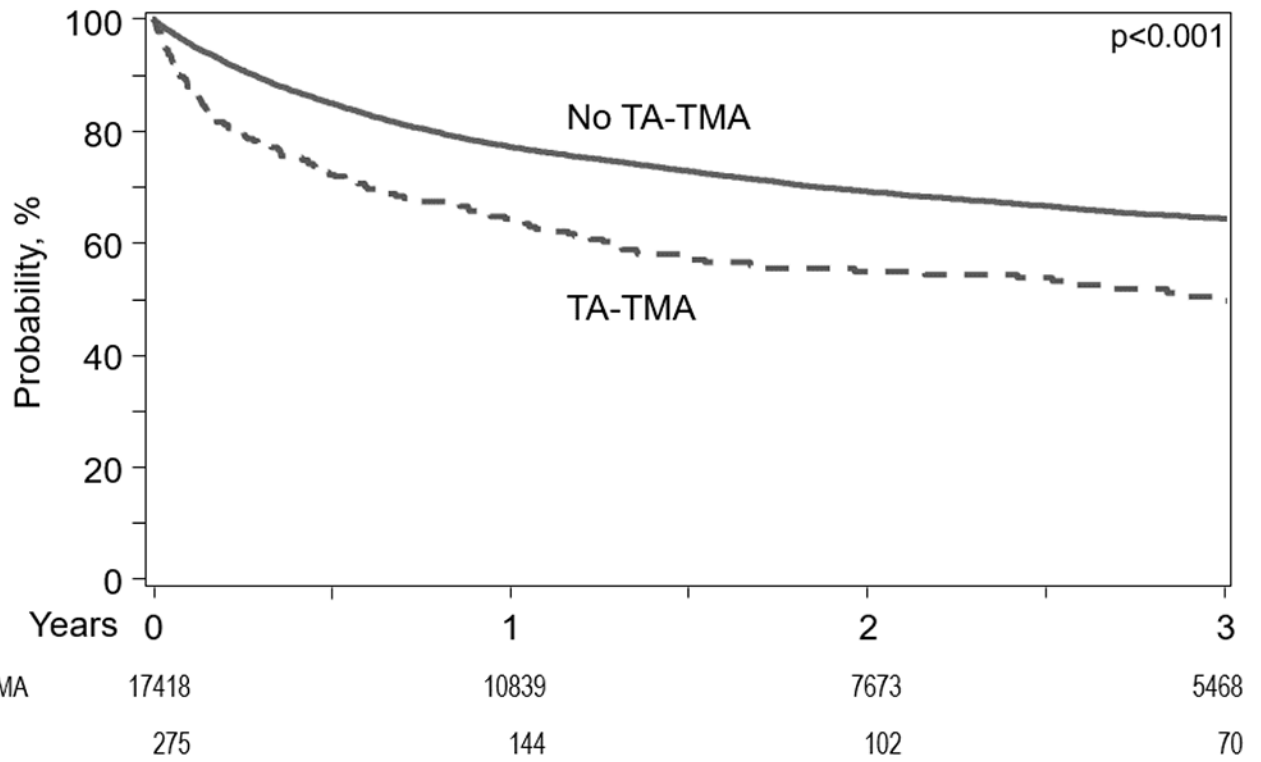Landmark Analysis at 6 months following allo-HCT showing survival between TA-TMA and no TA-TMA

Table 1.

Baseline characteristics of patients who underwent allo-HCT between 2008-2016

Variable	N=23665 (%)
Median age at HCT, years (range)	49 (1-83)
Male gender	13928 (59)
Race	
Caucasian	18752 (79)
African-American	2148 (9)
Others	1835 (8)
Missing	930 (4)
Karnofsky score	
90	15272 (65)
<90	7909 (33)
Missing	484 (2)
HCT-CI (excluding renal condition)	
0	8648 (37)
1	3222 (14)
2	2724 (12)
3	8322 (35)
Missing	749 (3)
Pre-conditioning kidney function	
Decreased (GFR<60)	1848 (8)
Normal (GFR 60)	20667 (87)
Missing	1150 (5)
Disease [*]	
Malignant	20847 (88)
Non-malignant	2818 (12)
Donor/recipient CMV status	
Both negative	8652 (37)
Any positive	14824 (63)
Missing	189 (<1)
Type of donor	
HLA-identical sibling	5963 (25)
Other related	2439 (10)
Matched URD (8/8)	8022 (34)
Partially matched URD (7/8)	1919 (8)
Mismatched URD (<7/8)	119 (<1)
URD, HLA match unknown	413 (2)
CB 6/6	538 (2)

Variable	N=23665 (%)
CB 5/6	1860 (8)
CB <5/6	1672 (7)
CB, HLA match unknown	692 (3)
Missing	28 (<1)
Donor-recipient ABO match	
Matched	11836 (50)
Minor Mismatch	4922 (21)
Major Mismatch	6018 (25)
CB - recipient A	85 (<1)
CB - recipient B	37 (<1)
CB - recipient AB	15 (<1)
CB - recipient O	111 (<1)
CB - recipient ABO unknown	10 (<1)
Missing	631 (3)
Prior auto-HCT	
No	22450 (95)
Yes	1089 (5)
Missing	116 (<1)
Graft type	
Bone marrow	4732 (20)
Peripheral blood	14171 (60)
CB	4762 (20)
Conditioning regimen and intensity	
Myeloablative TBI	5522 (23)
Myeloablative Bu based	7132 (30)
Other myeloablative	701 (3)
RIC/NMA	10279 (43)
Missing	31 (<1)
GVHD prophylaxis [**]	
CNI + post-Cy	1412 (6)
CNI + Siro (no post-Cy)	1791 (8)
Siro (no CNI or post-Cy)	166 (<1)
Csa (no Tac, Siro, or post-Cy)	6452 (27)
Tac (no Csa, Siro, or post-Cy)	12112 (51)
Other prophylaxis strategies	1732 (7)
ATG/ alemtuzumab	
No ATG or alemtuzumab	15041 (64)
ATG alone	7462 (32)
Alemtuzumab alone	1146 (5)

Variable	N=23665 (%)
ATG + alemtuzumab	16 (<1)
Year of transplant	
2008-2012	11222 (47)
2013-2016	12443 (53)
Median follow-up of survivors (range), months	37 (3-110)

Abbreviations: HCT- hematopoietic cell transplantation, HCT-CI- HCT comorbidity index, GFR- glomerular filtration rate, CMV – cytomegalovirus, HLA - human leukocyte antigen, URD-unrelated donor, CB- cord blood, auto- autologous, Bu-busulfan, TBI-total body irradiation, RIC/NMA- reduced-intensity conditioning/non-myeloablative conditioning, GVHD- graft-versus-host disease, Cy-Cyclophosphamide, CNI-calcineurin inhibitor, Tac- tacrolimus, Csa-cyclosporine, Siro-sirolimus, ATG- anti-thymocyte globulin

*
Disease breakdown is shown in Supplemental Table S4

Table 2.

Cox regression models of the impact of TA-TMA on overall survival and renal failure/need for dialysis, using TA-TMA as time-dependent covariate

Outcome	Level	N	HR	Lower 95% CI	Upper 95% CI	Pwp	Overall p-value
Overall survival							<0.001
	No TA-TMA	22944	1.00				
	TA-TMA, all patients	653	3.09	2.79	16.34	<0.001	
	TA-TMA, no plasmapheresis	499	2.47	2.20	2.78	<0.001	
	TA-TMA, plasmapheresis	154	4.14	3.44	4.99	<0.001	
Need for RRT							<0.001
	No TA-TMA	21939	1.00				
	TA-TMA, all patients	619	7.12	5.74	311.64	<0.001	
	TA-TMA, no plasmapheresis	467	3.81	2.87	5.05	<0.001	
	TA-TMA, plasmapheresis	152	14.92	10.90	20.42	<0.001	

Abbreviations: HR - hazard ratio, CI - confidence interval, TA-TMA - transplant associated thrombotic microangiopathy; N - number; RRT - renal replacement therapy, pwp - pairwise p-value

[*] Adjusted for age, race, KPS, kidney function at baseline, disease, disease status, donor type, prior auto-HCT, use of ATG/ alemtuzumab, year of TX, GVHD prophylaxis, conditioning, and graft type.

Table 3:

Causes of Death

Causes of death, N (%)	No TMA (n=10644)	TMA (n=429)
Organ failure	**1848 (17)**	**104 (24)**
Multisystem organ failure	359	25
Pulmonary failure	413	23
ARDS	228	15
IPS	117	7
Pneumonitis	65	1
DAD or other pulmonary syndrome	23	1
Cardiac failure	220	12
Liver failure	62	3
VOD/SOS	99	4
Renal failure	38	6
CNS failure	37	1
Other organ failure or not specified	187	6
Primary Disease	**4738 (45)**	**96 (22)**
Infection	**1715 (16)**	**87 (20)**
Graft versus Host disease	**1275 (12)**	**81 (19)**
Hemorrhage or vascular	**266 (3)**	**35 (8)**
Second malignancy	224 (2)	3 (<1)
Graft rejection/failure	151 (1)	2 (<1)
Other/unknown	427 (4)	21 (5)

Abbreviations: IPS - Idiopathic pulmonary syndrome, DAD – diffuse alveolar damage, ARDS – acute respiratory distress syndrome, VOD – veno-occlusive disease, SOS - sinusoidal obstruction syndrome, CNS – central nervous system