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Graft-versus-tumor effects

Transplant-associated microangiopathy (TAM) in recipients of allogeneic hematopoietic stem cell transplants

MT Martinez, Ch Bucher, G Stussi, D Heim, A Buser, DA Tsakiris, A Tichelli, A Gratwohl and JR Passweg

Hematology Division, Basel University Hospitals, Basel, Switzerland

Summary:

We studied occurrence, risk factors and outcome of patients with transplant-associated microangiopathy (TAM) after allogeneic stem cell transplantation (HSCT). A total of 221 consecutive patients were transplanted between 1995 and 2002. TAM is defined as evidence of hemolysis and schistocytes in the first 100 days. Outcomes analyzed included TAM and overall survival. Of 221 patients, 68 had TAM. The cumulative incidence was 31 (25–38)% at 100 days. Patients with TAM had higher LDH, higher bilirubin, higher creatinine and more often neurologic symptoms. TAM was not associated with stem cell source, cyclosporine levels and was not more frequent in recent years. In multivariate analysis, risk factors for TAM included donor type, age, gender, ABO-incompatibility and acute graft-versus-host disease (aGvHD). In patients with TAM, 1-year survival was lower than in patients without TAM (27 ± 18% for TAM with high schistocyte counts; 53 ± 15% for TAM with low schistocyte counts; *vs* 78 ± 7% in patients without TAM; $P < 0.0001$). TAM was independently associated with mortality adjusting for donor type, age and aGvHD occurrence and severity. TAM is frequent after HSCT and is associated with mortality even after adjustment for aGvHD grade. Risk factors of TAM are similar to aGvHD. TAM may represent endothelial damage driven by donor–host interactions.

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Transplant-associated thrombotic microangiopathy (TAM) is a poorly defined complication after allogeneic hematopoietic stem cell transplantation (HSCT).[1–20] Thrombotic microangiopathy is characterized by systemic or intrarenal platelet aggregation and a microangiopathic hemolytic anemia, with red blood cell (RBC) fragmentation and a negative direct antiglobulin test. Increased platelet consumption leads to thrombocytopenia. Other clinical manifestations include fever, renal dysfunction and neurologic abnormalities as a consequence of systemic perfusion deficits. The classical form of thrombotic microangiopathy is thrombotic thrombopenic purpura (TTP), ascribed to the absence or lack of function of ADAMTS 13, a metalloprotease cleaving multimeric von Willebrand factor. This deficiency may be due to autoantibodies or congenital defects.[21–27] Other forms of thrombotic microangiopathy are associated with enteropathogenic *Escherichia coli* infections (hemolytic uremic syndrome), drugs, including CsA, or occur after transplant, that is, TAM. Reduced metalloprotease activity is not the pathophysiologic mechanism in TAM[25,28] and plasma exchange is generally ineffective.[4,29] There is no validated definition for this syndrome.[14] Outcome of this complication may be variable, but little is known about causes and factors determining outcome of affected patients.

Given the recent demonstration of endothelial cells as acute graft-versus-host disease (aGvHD) targets,[30] we hypothesized that TAM may represent a particular form of endothelial aGvHD. To investigate this, we undertook this retrospective cohort study to look at the incidence of and risk factors for TAM, specifically at the association with the use of peripheral stem cells as a stem cell source, and to describe outcome of patients with TAM.

Diagnosis of TAM is difficult as this occurs during a time when patients are subject to multiple complications such as conditioning regimen-related toxity, GvHD, and infections. Given the uncertainty of diagnosis of TAM we used evidence of hemolysis, and of red cell fragmentation to define TAM for this study.

Patients and methods

Patients

This is a retrospective analysis of the incidence, risk factors and outcome of patients with TAM after allogeneic HSCT, based on data from 221 consecutive patients, receiving a first allogeneic HSCT between 1995 and 2002 at a single center. All patients were included except for eight recipients

Correspondence: Dr JR Passweg, Hematology Division, Basel University Hospitals, Petersgraben 4, CH – 4031, Basel, Switzerland;
E-mail: jpassweg@uhbs.ch
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of syngeneic transplants and five patients with inadequate documentation. Patients were aged between 2 and 63 years (median 35). Patient characteristics are outlined in Table 1. All patients were followed for early complications, aGvHD, and TAM within 100 days after transplantation and longer for survival. Median follow up of surviving patients is 26 (3–99, range) months.

Definitions

TAM was defined as evidence of hemolysis in the presence of schistocytes in the blood smear. Blood smears were analyzed manually weekly, and parameters of hemolysis were measured daily. Hemolysis was defined arbitrarily as the combination of LDH 300 IU/l, bilirubin $\geqslant 25\,\mu$mol/l and a decrease in hemoglobin $\geqslant 10$ g/l. Schistocytes $\geqslant$2–5/hpf were used as the minimum criterion for the diagnosis of TAM. Patients with 5–10/hpf and higher schistocyte counts were classified as TAM with high numbers of schistocytes. Diagnostic criteria did not include thrombocytopenia, because it was almost universal, and neurological or renal dysfunction, as these were more varied.

Red cell engraftment was defined as time to two consecutive measures with reticulocytes $>1\%$, neutrophil engraftment was defined as time to neutrophil count $>0.5\times10^9$/l and platelet engraftment as time to platelets $>50\times10^9$/l. Acute GvHD was diagnosed and graded according to the Glucksberg criteria. Neurological dysfunction was defined as any new neurological abnormality (eg seizures, confusion, motor or sensory deficits). CsA trough levels were measured weekly. The highest trough levels in the first 100 days were recorded and the highest of three consecutive levels in the same range was used to define patients with high CsA levels. Variables associated with occurrence and severity of TAM and aGvHD are shown in Table 2 describing the clinical course up to 100 days post transplant.

Table 1 Patients characteristics

	N	*% or range*
N total	221	100%
Disease		
AML	58	26%
ALL	48	22%
CML	46	21%
Lymphoma/myeloma	32	14%
MDS/MPS	29	13%
Aplastic anemia	8	4%
Disease stage		
Early leukemia	73	33%
Advanced leukemia	79	36%
Age in years (median, range)	35	2–63
Male gender	122	55%
Donor–recipient gender match		
Male/male	78	35%
Male/female	55	25%
Female/female	44	20%
Female/male	44	20%
Donor–recipient ABO compatibility		
Identical	126	57%
Major barrier	46	21%
Minor barrier	42	19%
Bidirectional barrier	7	3%
Donor–recipient relationship		
Identical sibling	150	68%
Unrelated	43	19%
Mismatched relatives	28	13%
Source of stem cell		
Peripheral blood	147	66%
Bone marrow	74	34%
Conditioning regimen		
Cy/VP16/TBI	142	64%
Cy/ATG	33	15%
Fludarabine/TBI	29	13%
Bu/Cy	17	8%
Conditioning intensity		
Reduced intensity conditioning	39	18%
GvHD prophylaxis		
CsA/MTX	124	56%
CsA	41	19%
CsA/MMF	26	12%
T-cell depletion	30	13%

MDS = myelodysplastic syndromes; MPS = myeloproliferatives syndromes; VP16 = Etoposide; ATG = anti-thymocyte globulin; MMF = mycophenolate mofetil.

Outcomes

The major outcomes analyzed were the cumulative incidence and severity of TAM in the first 100 days post transplant. Other outcomes included aGvHD and 1-year survival in patients with and without TAM.

Statistical analysis

Variables were compared in patients with and without TAM by the Mann–Whitney U tests or χ^2 tests where appropriate. The cumulative incidence of TAM and acute GvHD was calculated using death without TAM or death without aGvHD as competing risks, as appropriate. The 1-year survival was assessed using the Kaplan–Meier estimator and univariate comparisons between groups were by the log-rank test. Risk factors analyzed included patient and disease characteristics, such as age, gender, disease, disease stage; transplant characteristics, such as year of transplant, donor type, ABO barrier, donor–recipient gender match, conditioning intensity, stem cell source and dose; post transplant GvHD prophylaxis, and early post transplant characteristics, such as the presence and grade of aGvHD and CsA levels. Cox proportional hazards regression models were used for the multivariate analysis of risk factors for TAM and survival. To account for onset times of GvHD and TAM the proportional hazards regression models were built, using time-dependent covariates for aGvHD and TAM in a way that patients were in the group without TAM and without aGvHD at the time of transplant and switched to the group with TAM and aGvHD, respectively, at the time of onset of these complications.

Table 2 Comparison of post transplant course of patients with and without TAM

	No TAM	*TAM*	*P*
Patients (*n*)	153 (69%)	68 (31%)	
Time to onset TAM in days (median, range)		27 (4–91)	
Hemolysis (bilirubin $>25\,\mu$mol/l, and LDH >300 U/l and decrease in Hb)	32 (21%)	68 (100%)	0.0001
LDH max (U/l) (median, range)	635 (262–7625)	1261 (519–11530)	0.0001
Bilirubine max (μmol/l) (median, range)	21 (5–422)	75 (17–1333)	0.0001
Creatinine max (μmol/l) (median, range)	137 (19–560)	192 (46–613)	0.0001
Schistocytes (median)	0/hpf	2–5/hpf	0.0001
RDW (%) max (median, range)	20 (14–35)	25 (17–41)	0.0001
MCV max (median, range)	97 (81–126)	101 (84–116)	0.037
Circulating erythroblasts (median, range)	0.01 (0–9)	0.18 (0–9)	0.001
aPTT (median, range)	35 (24–98)	39 (24–180)	0.013
Max reticulocytes count within 100 days	149 (0–841)	198 (47–159)	0.0002
Platelet nadir $\times 10^9$/l	12 (1–25)	9 (3–14)	0.001
Neutrophil engraftment (median, range)	15 (1–49)	14 (1–59)	0.19
Platelet engraftment (median, range)	13 (1–205)	14 (1–120)	0.783
Red cell engraftment (days (median, range))	9 (1–156)	11 (1–60)	0.256
Highest CsA trough levels (median, range)	328 (79–1469)	341 (142–1474)	0.73
Transfusions requirements			
Platelets (median, range)	4 (0–52)	9 (0–53)	0.0001
Erythrocytes (median, range)	6 (0–58)	16 (0–61)	0.0001
Acute GvHD			0.001
no GvHD	46 (30%)	11 (16%)	
Grade I	33 (22%)	12 (18%)	
Grade II	49 (32%)	17 (25%)	
Grade III	19 (12%)	17 (25%)	
Grades IV	6 (4%)	11 (16%)	
aGvHD time to onset ($\geqslant$grade II (days; median))	12 (3–96)	12 (4–51)	0.09
Fever	122 (80%)	53 (78%)	0.92
Neurological symptoms	37 (24%)	27 (40%)	0.02
Renal failure	57 (37%)	40 (59%)	0.03
Cause of death			
Relapse/progression (until 2004)	30 (20%)	13 (19%)	0.93
GvHD	10 (7%)	20 (29%)	0.009
Infection	8 (5%)	8 (12%)	0.78
VOD	2 (1%)	3 (4%)	0.55

LDH = lactate dehydrogenase; RDW = red cell distribution width; MCV = red blood cell volume; Erythroblast = counted as $n/200$ nucleated cells 10^9/l; aPTT = activated partial thromboplastin time; VOD = veno-occlusive disease.

Results

Patient and disease characteristics are shown in Table 1. Patients had mainly hematologic malignancy and the median age was 35 (range, 2–63) years. In all, 122 were male (55%) and 99 were female (45%) patients. The cohort included patients receiving transplants from identical siblings (68%), unrelated donors (19%) and mismatched family donors (13%). Stem cell source was peripheral blood (66%) with a median infused nucleated cells of 9.32×10^8/kg body weight and bone marrow (34%) with a median infused nucleated cells of 3.56×10^8/kg body weight.

Table 2 describes early post transplant events associated with TAM and aGvHD. Using the definition mentioned above TAM was observed in 68 patients with an incidence of 31% (25–38) at 100 days. A total of 25 patients experienced severe TAM as defined as TAM with high numbers of schistocytes (11%). Median time of onset of TAM was 27 (4–91) days post transplant. Neurological symptoms were manifest in 64 (29%) and renal failure defined as doubling in creatinine values in 97 (44%) of all patients. The median follow-up time of surviving patients was 26 (3–99) months. Of note, none of the seven recipients of syngeneic HSCT transplanted during the same time period and not included in the analysis had TAM ($P = 0.1$).

As expected, patients with TAM had significantly higher LDH, bilirubin, schistocytes and creatinine levels as compared to patients without TAM. They had more often renal failure or neurologic symptoms and required more often red cell and platelet transfusions. Time to neutrophil, RBC, and platelet engraftment was similar among the groups. Patients with TAM also had higher counts of circulating erythroblasts counts suggesting a higher RBC turnover, and longer activated partial thromboplastin time, possibly reflecting consumption of coagulation proteins.

There was a significant trend for more TAM with higher grades of aGvHD ranging from 19% TAM in patients without aGvHD, to 27, 26, 47, and 65% in patients with grade I, II, III, and IV aGvHD, respectively (Table 3).

The cumulative incidence of TAM was higher in recipients of unrelated or mismatched related donor transplants, in female patients and in patients with major and bidirectional blood group barrier, whereas the

Table 3 Cumulative incidence of TAM by day 100 by risk factors

	CI of TAM	*P*
TAM, all patients	0.31 (0.25–0.38)	
Age		0.14
<10 years	0.14 (0.05–0.39)	
10–40 years	0.31 (0.23–0.41)	
>40 years	0.35 (0.27–0.47)	
Donor type		0.0001
Identical sibling	0.23 (0.17–0.30)	
Unrelated	0.58 (0.45–0.75)	
Mismatched relatives	0.32 (0.19–0.55)	
Recipient gender		0.02
Male	0.24 (0.17–0.33)	
Female	0.39 (0.31–0.50)	
Donor recipient gender match		0.07
Male/male	0.26 (0.18–0.38)	
Male/female	0.36 (0.26–0.52)	
Female/female	0.43 (0.31–0.61)	
Female/male	0.21 (0.12–0.37)	
Stem cell source		0.89
BM	0.32 (0.23–0.45)	
PB	0.30 (0.23–0.38)	
Donor–recipient ABO compatibility		0.02
Identical	0.23 (0.17–0.32)	
Minor barrier	0.36 (0.24–0.54)	
Major barrier	0.46 (0.34–0.63)	
Bidirectional	0.43 (0.18–1.00)	
GvHD prophylaxis		0.12
CsA	0.22 (0.12–0.39)	
CsA/MTX	0.37 (0.30–0.47)	
CsA/MMF	0.17 (0.07–0.37)	
T-cell depletion	0.31 (0.17–0.55)	
Year of transplant		0.53
< 2000	0.33 (0.26–0.43)	
⩾2000	0.28 (0.21–0.38)	
Maximal CsA trough levels		0.69
Less than 500 μmol/l	0.30 (0.24–0.39)	
More than 500 μmol/l	0.34 (0.23–0.51)	
Acute GvHD		0.0004[a]
No GvHD	0.19 (0.11–0.33)	
Grade I	0.27 (0.17–0.44)	
Grade II	0.26 (0.17–0.39)	
Grade III	0.47 (0.34–0.67)	
Grades IV	0.65 (0.46–0.92)	
CMV infection		0.37
Yes	0.37 (0.26–0.52)	
No	0.29 (0.23–0.37)	
Central venous line infection		0.03
Yes	0.44 (0.32–0.62)	
No	0.28 (0.22–0.35)	
Clostridium difficile positive diarrhea		0.04
Yes	0.53 (0.34–0.83)	
No	0.29 (0.23–0.36)	

BM = bone marrow; PB = peripheral blood; MMF = mycophenolate mofetil.
[a]Log rank test for trend.

incidence did not differ by disease, disease stage, stem cell source, cell dose, conditioning regimen, donor–recipient gender-matching year of transplant, and CsA trough levels. Patients with clostridium toxin-positive diarrhea and central venous line infection had TAM more frequently than patients without.

The cumulative incidence of grades II–IV aGvHD by day 100 was 53 (46–59)%. Median time to onset was 12 days post transplant. Patients without TAM had a lower incidence of aGvHD, 44 (36–53)%, than those with TAM 63 (52–77)%; $P = 0.01$. The highest incidence of aGvHD was seen in patients with TAM with high schistocytes 78 (63–97)%; $P < 0.0004$.

Table 4a and b shows results of multivariate analysis of TAM and survival. Covariates significantly associated with TAM risks were donor type, highest risks were with unrelated donors, patient age with a graded increase in risk by age, female gender and major/bidirectional ABO-blood group barrier between donor and recipient. Figures 1 and 2 show the cumulative incidence of TAM by donor type and gender.

Figure 3 shows survival of patients with no TAM, TAM with low schistocyte counts and TAM with high schistocyte counts. Mortality risks (Table 4b) were higher in recipients of mismatched related donor stem cells, grades III–IV aGvHD conferred mortality risks as well as TAM even after adjustment for effects of acute GvHD. The table also shows mortality risks separately for patients with TAM with low and high schistocyte counts showing highest mortality risks associated with high schistocyte counts.

Discussion

This retrospective single center study, analyzing a cohort of 221 consecutive patients receiving an allogeneic HSCT, shows that according to a definition of TAM including evidence of hemolysis and RBC fragmentation, TAM was observed with a considerable incidence of 31 (25–38)% by day 100 post transplant. Median time of onset was 27 (6–76) days. As expected TAM was associated with renal dysfunction and neurologic manifestation, but this was not observed in all patients.

TAM was more frequent in older patients and in recipients of unrelated donor transplants, both risk factors for aGvHD. TAM was also more frequent in female patients and in recipients of grafts with a major or bidirectional ABO blood group mismatch. There was no association of TAM with year of transplant, with stem cell source or dose, with disease and disease stage, and high CsA trough levels bore no relationship with TAM incidence. TAM was not associated with transplant technique, such as GvHD prophylaxis or conditioning regimen. TAM did not correlate with CMV infection but was more frequent in patients with *Clostridium difficile* positive diarrhea or with central line infection. TAM correlated with GvHD severity, the higher the aGvHD grade, the more the patients who had TAM. Patients with TAM had higher mortality, and in multivariate analysis the impact of TAM was of equal magnitude as the impact of grades III–IV aGvHD. There was increasing mortality

Table 4 Multivariate analysis of risk factors for (a) TAM and (b) survival

(a) TAM	*RR of TAM (95% CI)*	*P*
Donor type		0.0001
Identical sibling	1.00	
Unrelated	3.05 (1.69–5.54)	
Mismatched relatives	2.42 (1.12–5.22)	
Age (years)		0.003
<10	1.00	
10–40	3.31 (0.99–11.08)	
>40	6.49 (1.87–22.59)	
Recipient gender		0.02
Male	1.00	
Female	1.76 (1.08–2.87)	
Donor–recipient ABO compatibility		0.001
Minor or no ABO barrier	1.00	
Major/bidirectional ABO barrier	2.40 (1.42–4.05)	
Acute GvHD		
aGvHD grade 0 or I	1.00	
Grade II GvHD	1.98 (0.99–3.95)	0.053 (*vs* grades 0–I)
Grade III/IV	4.39 (2.39–8.07)	0.001 (*vs* grades 0–I)
(b) Survival	*RR of death (95% CI)*	*P*
Donor type		0.034
Identical sibling	1.00	
Unrelated	1.01 (0.60–1.71)	
Mismatched relatives	2.11 (1.18–3.75)	
Acute GvHD		0.0001
None or grades I/II	1.00	
Grade III/IV	3.32 (2.11–5.21)	
TAM		0.0001
No TAM	1.00	
Any grade of TAM	3.14 (2.05–4.86)	
Graded TAM		
TAM with low schistocyte counts	2.44 (1.48–4.02)	0.0001 (*vs* no TAM)
TAM with high schistocyte counts	4.92 (2.84–8.53)	0.0001 (*vs* no TAM)

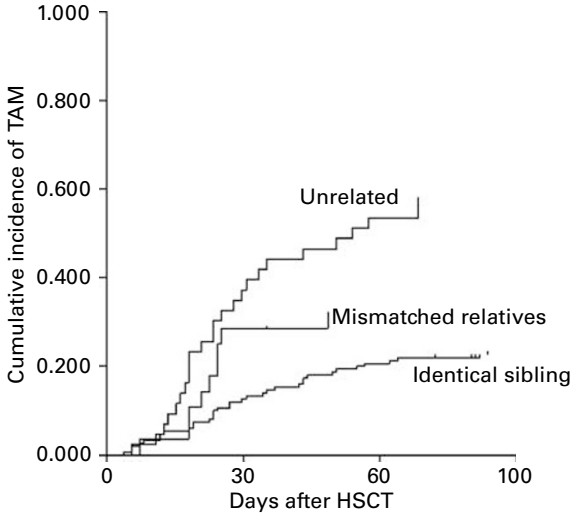

Figure 1 Cumulative incidence of transplant-associated microangiopathy (TAM) within 100 days post transplant by donor type; $P = 0.0001$.

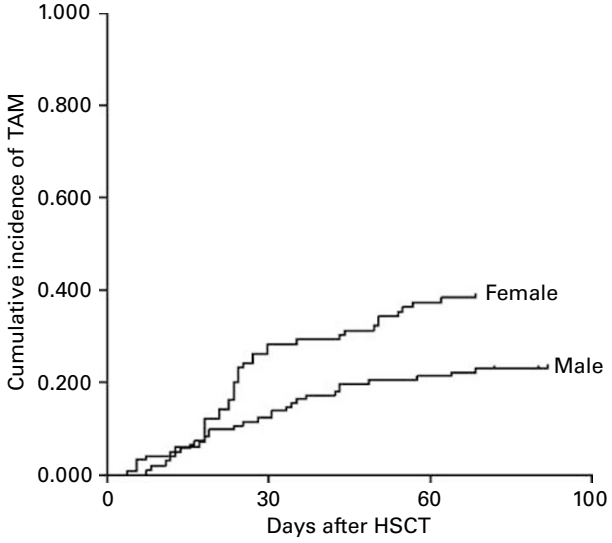

Figure 2 Cumulative incidence of transplant-associated microangiopathy (TAM) within 100 days post transplant by recipient gender; $P = 0.02$.

with TAM severity comparing patients with TAM with high schistocytes counts to patients with TAM with low schistocyte counts.

Reported incidence rates in the literature vary considerably, ranging from 0 to 74%.[14,31] This wide range may be explained by differing diagnostic criteria of TAM used in various studies,[14] and probably by differences in patients, disease and transplant characteristics. In a recent review, 24 of 35 studies reporting five or more patients with TAM included both RBC fragmentation and serum LDH in the definition of TAM.[14] We included in our definition evidence of hemolysis and RBC fragmentation. Assessment of hemolysis is not interpreted with ease as these enzymes, liberated by RBC destruction, are not specific but are also seen with GvHD-mediated cell destruction and infectious complications. Other variables often used to define TAM such as thrombocytopenia are equally problematic as most patients with a difficult clinical post transplant course, be it GvHD, infection or toxicity will tend to be thrombocytopenic.[12] Other studies included neurologic abnormality and renal failure in TAM definition.[14,20,32] As these reflect end-organ damage induced by severe forms of this syndrome we chose not to include them to allow for analysis of milder forms of the disease. It is likely that the incidence of TAM would have been lower with more stringent diagnostic criteria.

Given the heightened clinical awareness, we had expected a higher incidence of TAM in more recent years and we had suspected that this increased frequency was associated with the increased use of peripheral stem cells as a stem-cell source.[16] We did not find more TAM in recent years nor with use of peripheral stem cells. Peripheral stem cells have been shown to be associated with more chronic but not

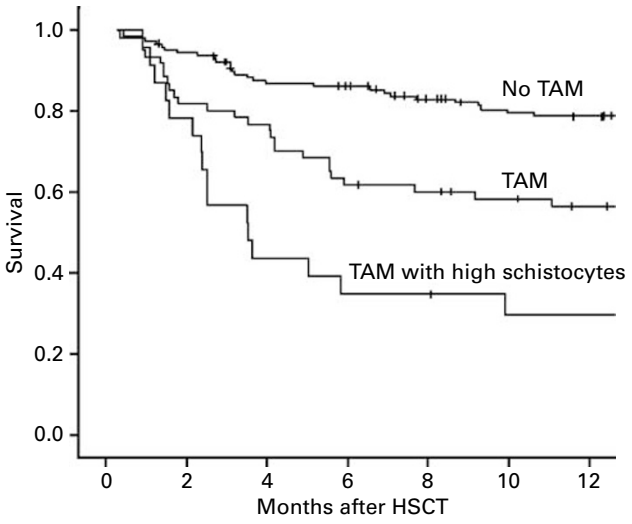

Figure 3 Probability of survival in the first 12 months after HSCT in patients with or without transplant-associated microangiopathy (TAM). The 1-year survival in patients with TAM (27±18% TAM with high schistocyte counts, 53±15% TAM with low schistocyte counts) was lower than in patients without TAM (78±7%); $P<0.0001$.

with more aGvHD, and TAM is generally an early event after HSCT.[33]

The higher risk of TAM observed among female patients has also been observed in other studies.[6,11,12,16] This present study confirms this gender effect but the pathophysiology remains unresolved, hypotheses include a role of hormones, oral contraceptives, sensitization by pregnancy or other hitherto unknown factors. The increased risk for TAM was only observed with female patients, whereas stem cell transplants from female donors were not associated with a higher risk for TAM suggesting that it is not an effect of the donor stem cells, but rather of the host environment. Higher TAM risks in recipients of stem cells from a donor with major/bidirectional ABO incompatibility may be explained by hemolysis induced by preformed antibodies, associated with blood group changes as TAM. It is known that immune-mediated hemolysis may sometimes result in RBC fragmentation. Total body irradiation (TBI) has been previously associated with TAM[13,32,34–36] This as well as other studies[3,5,8] could not confirm an impact of TBI.

Calcineurin inhibitors are known to cause microangiopathy and several studies[17,31,37] have attributed TAM to CsA toxicity, whereas others have described TAM in patients off CsA.[11] We could not analyze CsA use *vs* none, as all patients analyzed had CsA (with the exception of twins). We could not detect any difference in TAM incidence in patients with high or low trough levels of CsA.[2,3,11,17] This does not exclude a causative role of CsA in susceptible patients, but there is no obvious relationship with plasma levels. This is of importance as CsA is withdrawn in patients with TAM in many centers; others switch treatment to alternative drugs.[37–39]

The higher incidence of *C. difficile* positive diarrhea in patients with TAM *vs* no TAM is of interest, but remains unexplained. Pseudomembraneous colitis may be associated with RBC fragmentation and the hemolytic uremic syndrome in patients with *C. difficile* colitis has been described.[40] Similarly with central venous line infection it is probably septicemia associated with schistocytes that qualifies patients for the diagnosis of TAM given the definition used. Alternatively, TAM may be precipitated by infectious complications similar to GvHD.

The strongest risk factors for TAM were age and HSCT from unrelated donors,[1,4,6–8,15,20] both risk factors for aGvHD. TAM was correlated with aGvHD severity.[31] The median time to TAM onset was longer than to aGvHD onset (27 *vs* 12 days). We hypothesized that TAM may represent as a particular form of aGvHD associated with endothelial damage possibly induced by host T cells. In a recent study host endothelial cells were reported as targets of alloreactive donor cytotoxic T lymphocytes leading to decreased microvessel density in patients with chronic GvHD.[30] Further evidence for an allogeneic effect is the absence of TAM in identical twin transplants in this series and the absence of TAM in reported series of autologous HSCT.[3,12] Patients meeting criteria of TAM but without aGvHD were more likely to have received grafts with major or bidirectional ABO blood group barrier ($P<0.025$), further supporting this hypothesis. Increased soluble vascular cell adhesion molecules reported in GvHD and TAM[41] as markers of endothelial damage may represent a common pathophysiologic pathway. Elevated number of circulating endothelial cells may be useful for diagnosis.[42] Increased circulating erythroblasts, observed in patients with TAM (Table 2), may represent a deranged marrow–blood barrier. The longer aPTT in patients with TAM possibly reflects activation and consumption of coagulation proteins. This is in contrast to a study reporting no such difference.[43] Activated coagulation would fit the hypothesis of endothelial damage as the cause for TAM. GvHD prophylaxis had no influence on TAM, but it is of interest, that the lowest incidence of TAM was in patients receiving a T-cell-depleted transplant. To further test these hypotheses, measures of endothelial damage may be helpful.[2,3,41]

Plasma exchange has been used extensively to treat TAM but is now not considered to be effective. Plasma exchange is used in classical TTP and this use is in accordance with today's understanding of its pathophysiology.[25] A previous study had found higher mortality in patients receiving plasma exchange[14] possibly due to patients with severe disease being more likely to receive this form of treatment.

The 1-year survival in our cohort study was 78±7% for patients without TAM and 27±18% for patients with TAM with high schistocyte counts, and 53±15% for patients with TAM with low schistocyte counts. This has been observed by other investigators as well.[12] Schistocyte counts may be used quantitatively for prognostic impact. Mortality rates reported in the literature vary from 0 to 100%.[14,36] In this study the impact of TAM on mortality was of similar magnitude as the impact of grades III–IV aGvHD (Table 4b).

This cohort study of 221 patients with allogeneic HSCT showed a TAM incidence of 31%. Unrelated donor, age, major/bidirectional donor–recipient ABO incompatibility, female gender and aGvHD were risk factors. Mortality of this complication remains high. Risk factors of TAM are similar to aGvHD. TAM may represent endothelial damage driven by donor–host interactions.

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