Bone Marrow Transplantation (2010) 45, 689–693
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ORIGINAL ARTICLE

Comparison of thrombotic microangiopathy after allogeneic hematopoietic cell transplantation with high-dose or nonmyeloablative conditioning

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The role of conditioning intensity on occurrence of thrombotic microangiopathy (TMA) after allogeneic hematopoietic cell transplantation (HCT) has remained unclear thus far. Here, we retrospectively compared the incidence of TMA in patients given allogeneic hematopoietic stem cells after either nonmyeloablative ($n = 176$) or high-dose ($n = 111$) conditioning. The 1-year cumulative incidence of TMA was 13% in nonmyeloablative recipients versus 15% in high-dose conditioning recipients ($P = 0.5$). In multivariate Cox analysis, occurrence of grade 3–4 acute graft-versus-host disease (GVHD) (hazard ratio (HR) = 2.3, $P < 0.001$), older age (HR = 1.01, $P = 0.045$), and unrelated donors (HR = 1.6, $P = 0.01$) were each associated with a higher risk of TMA, whereas nonmyeloablative conditioning was associated with a lower risk of TMA (HR = 0.6, $P = 0.01$). We conclude that acute GVHD, age, donor type, and conditioning intensity might have a role in the physiopathology of TMA after allogeneic HCT.

Bone Marrow Transplantation (2010) **45,** 689–693; doi:10.1038/bmt.2009.230; published online 31 August 2009
Keywords: hematopoietic cell transplantation; thrombotic microangiopathy; nonmyeloablative; GVHD

Introduction

Post-transplant thrombotic microangiopathy (TMA) is an important complication of allogeneic hematopoietic cell transplantation (HCT).[1] This syndrome associates microangiopathic hemolysis with renal and/or neurologic impairment. It has been proposed that endothelial injury might contribute to the occurrence of TMA after allogeneic HCT.[1] The main mechanisms involved in endothelial injury after allogeneic HCT include high-dose chemotherapy, high-dose radiotherapy, and acute graft-versus-host disease (GVHD). Other factors that have been associated with TMA after allogeneic HCT include viral or fungal infections, unrelated donor, ABO incompatibility, and postgrafting immunosuppression with sirolimus combined with a calcineurin inhibitor.[1,2]

The recent development of nonmyeloablative conditioning regimens has permitted performing allogeneic transplantation in older patients, those with medical comorbidities, and those who had failed a high-dose transplant.[3–6] This approach relies nearly exclusively on the destruction of malignant cells by donor T cells and NK cells through graft-versus-tumor effects.[7,8]

In this study, we retrospectively assessed the role of conditioning intensity on TMA occurrence after allogeneic HCT.

Patients and methods

Patients, conditioning regimen, and postgrafting immunosuppression

Data from 287 patients given allogeneic bone marrow or peripheral blood stem cells after myeloablative or nonmyeloablative conditioning from January 2000 to July 2008 were retrospectively analyzed. Their characteristics are listed in Table 1. Although there is no consensus on what constitutes nonmyeloablative conditioning versus not,[9] we defined nonmyeloablative conditioning in this study as conditioning that could be performed entirely in the outpatient setting in most patients. High-dose conditioning regimens were based on high-dose (single dose of 8 Gy or 6×2 Gy) total body irradiation (TBI) ($n = 91$), intermediate (8 mg/kg, $n = 4$) or high-dose (16 mg/kg, $n = 8$) busulfan, or high doses of other alkylating agents ($n = 8$). Nonmyeloablative conditioning regimens consisted of 2 Gy TBI alone ($n = 3$), fludarabine 90 mg/m^2 plus 2 Gy TBI ($n = 113$), fludarabine 90 mg/m^2 plus 2×2 Gy TBI ($n = 17$), or fludarabine 90 mg/m^2 plus cyclophosphamide 3 g/m^2 ($n = 15$). In the high-dose group, postgrafting immunosuppression consisted in cyclosporine alone for 56 patients receiving CD34- or CD133-selected grafts. For the remaining 55 patients receiving unmanipulated grafts, postgrafting immunosuppression included tacrolimus plus mycophenolate mofetil ($n = 4$), cyclosporine alone ($n = 10$), or cyclosporine plus short methotrexate ($n = 41$, including 7 receiving additional anti-thymocyte globulin). In the

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Received 9 April 2009; revised 23 July 2009; accepted 26 July 2009; published online 31 August 2009

Table 1 Patients' characteristics

	Myeloablative conditioning (n = 111)	*Nonmyeloablative conditioning (n = 176)*
Median age	42 (4–66)	57 (10–72)
Gender: male/female	67/44	117/59
Diagnostic; no. of patients (%)		
AML	48 (43.2)	25 (14.2)
ALL	11 (9.9)	1 (0.6)
CML	7 (6.3)	5 (2.8)
CLL	3 (2.7)	16 (9.1)
Lymphoma	17 (15.3)	46 (26.1)
MDS et MPD	13 (11.7)	39 (22.2)
MM	4 (3.6)	35 (19.9)
Non-malignant	8 (7.2)	0 (0)
RCC	0 (0)	9 (5.1)
Donor; no. of patients (%)		
HLA-identical sibling	58 (52.3)	56 (31.8)
Unrelated 6/6 identical	42 (37.8)	109 (61.9)
$\geqslant$1/6 HLA-mismatched donors	11 (9.9)	11 (6.3)
Prior transplantation; no. of patients (%)	10 (9)	97 (55.1)
Conditioning regimen; no. of patients (%)		
High-dose TBI-based regimen	91 (82)	0 (0)
Busulfan-based regimen	12 (10.8)	0 (0)
Miscellaneous	8 (7.2)	0 (0)
TBI 2 Gy	0 (0)	31 (17.6)
Fludarabine 90 mg/m^2 + TBI 2 Gy	0 (0)	113 (64.2)
Fludarabine 90 mg/m^2 + TBI 4 Gy	0 (0)	17 (9.7)
Fludarabine 90 mg/m^2 + cyclophosphamide	0 (0)	15 (8.5)
Immunosuppressive regimen; no. of patients (%)		
CD34/CD133 selection + CSP	56 (50.5)	7 (+ MMF)[11]
CSP alone	10 (9)	0 (0)
CSP + MTX	34 (30.6)	0 (0)
CSP + MTX + ATG	7 (6.3)	0 (0)
MMF + CSP/tacrolimus	4 (3.6)	169 (96)
Graft source: bone marrow/PBSC; no. of patients (%)	9 (8.1)/ 102 (91.9)	2 (1.1)/ 174 (98.9)
ABO Compatibility; no. of patients (%)		
Identical	64 (57.7)	103 (58.5)
Major mismatch	26 (23.4)	47 (26.7)
Minor mismatch	27 (24.3)	35 (19.9)
Acute GVHD; no. of patients (%)		
Grade 0–1	82 (73.9)	106 (60.2)
Grade 2	14 (12.6)	44 (25)
Grade 3–4	15 (13.5)	26 (14.8)
TMA; no. of patients (%)	17 (15.3)	25 (14.2)
Median time of onset (days)	54 (0–256)	49 (18–519)
Median duration (days)	44 (4–120)	45 (5–246)
Neurologic signs; no. of patients (%)	12 (10.8)	14 (8)
Treatment; no. of patients (%)		
Stop calcineurin inhibitor	2 (1.8)	2 (1.1)
Shift calcineurin inhibitor	8 (7.2)	19 (10.8)
Plasma exchange	10 (9)	15 (8.5)
Rituximab	2 (1.8)	2 (1.1)
Vincristine	1 (0.9)	2 (1.1)
TMA as primary cause of death; no. of patients (%)	1 (0.9)	2 (1.1)
TMA as secondary cause of death; no. of patients (%)	4 (3.6)	6 (3.4)

Abbreviations: ATG = anti-thymocyte globulin; CSP = cyclosporine; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; MM = multiple myeloma; MPD = myeloproliferative disorder; RCC = renal cell carcinoma; TMA = thrombotic microangiopathy.

nonmyeloablative setting, postgrafting immunosuppression included mycophenolate mofetil combined with cyclosporine or tacrolimus in all patients. Fifty patients undergoing nonmyeloablative conditioning received CD8-depleted PBSC,[10] 119 unmanipulated PBSC, and 7 CD34-selected PBSC followed by CD8-depleted donor lymphocyte infusions.[11]

TMA definition

The following criteria[12] were used to define TMA: (1) RBC fragmentation and $\geqslant$2 schistocytes per high-power field on peripheral smear; (2) serum LDH increased above institutional baseline; and (3) concurrent renal (doubling of serum creatinine from baseline or 50% decrease in creatinine clearance from baseline) and/or neurologic dysfunction without other explanations. Diagnostic of TMA was carried out as follows: each patient with (1) evidence of schistocytes on peripheral smear; (2) serum LDH increased above institutional baseline; and (3) no apparent alternative etiologies were prospectively encoded in our clinical transplant database by YB or FB. EW reviewed all suspected cases of TMA and excluded cases that did not fulfill the above definition.

Statistical analyses

The cumulative incidence of TMA in all patients as well as in patients given high-dose or nonmyeloablative conditioning was calculated as described elsewhere.[13] Potential associations between HCT variables and TMA were assessed using the χ^2 tests or the Fisher's exact test whenever appropriate. A number of factors potentially associated with the occurrence of TMA were also assessed in a Cox model: grade 3–4 acute GVHD, donor type (related versus unrelated), patient age (modeled as a continuous linear variable), earlier HCT or not, tacrolimus or cyclosporine as GVHD prophylaxis, HLA compatibility (6/6 HLA-antigen matched versus other), major ABO mismatch, minor ABO mismatch, prior administration of sirolimus (given only as treatment for steroid-refractory acute or chronic GVHD in our patients), and conditioning regimen intensity. Statistical analyses were carried out with Graphpad Prism (Graphpad Software, San Diego, CA, USA) or with SAS version 9.1 (SAS Institute, Cary, NC, USA). The threshold significance level was 0.05.

Results

Incidence of TMA

The 1-year cumulative incidence of TMA was 13% in the nonmyeloablative setting versus 15% in the high-dose setting ($P = 0.5$). Median time after transplant for TMA diagnosis was 52 (range 0–519) days in all patients, 54 (range 0–256) days in the high-dose setting, and 49 (range 18–519) days in the nonmyeloablative setting. Mean ($\pm$ s.d.) % of schizocytes was 2.7 ± 1.0 in nonmyeloablative recipients versus 2.7 ± 1.1 in high-dose recipients ($P = 0.9$). Twelve percent of nonmyeloablative patients versus 59% of high-dose recipients were platelet transfusion-dependent at diagnosis of TMA ($P = 0.002$), whereas 68% of nonmyeloablative patients versus 88% of high-dose recipients were/became platelet transfusion-dependent after TMA ($P = 0.2$). Mean platelet levels at diagnosis of TMA in patients not requiring platelet transfusion were $58 \pm 36 \times 10^9$/l in nonmyeloablative patients versus $57 \pm 56 \times 10^9$/l in high-dose recipients ($P = 0.9$). Mean creatinine levels were 18 ± 10 mg/l in nonmyeloablative patients versus 17 ± 11 mg/l in high-dose recipients ($P = 0.8$).

Risk factors

The clinical factors predicting for TMA in univariate analyses are listed in Table 2. In multivariate Cox analyses (Table 3), occurrence of grade 3–4 acute GVHD (hazard ratio (HR) = 2.3, $P < 0.001$), higher patient age (HR = 1.01, $P = 0.045$), and unrelated versus related donors (HR = 1.6, $P = 0.01$) were each associated with a higher risk of TMA, whereas nonmyeloablative versus high-dose conditioning was associated with a lower risk of TMA (HR = 0.6, $P = 0.01$). There were no statistically significant associations between TMA and major (HR 0.8, $P = 0.2$) or minor (HR 1.2, $P = 0.2$) ABO mismatch between recipients and donors, $\geqslant 1/6$ HLA-antigen mismatches or not (HR 1.1, $P = 0.8$), prior HCT or not (HR = 0.8, $P = 0.3$), tacrolimus or cyclosporine as GVHD prophylaxis (HR 0.7, $P = 0.2$), or sirolimus administration or not (HR 0.8, $P = 0.6$) .

Median times to achieve 1×10^9 neutrophils/l and 100×10^9 platelets/l were 11 and 16 days, respectively, in patients without TMA versus 11 ($P = 0.8$) and 17 ($P = 0.7$) days, respectively, in patients who experienced TMA.

Outcomes of TMA

Of the 42 patients who experienced TMA, 30 were treated by changing immunosuppressive drugs alone ($n = 12$) or in combination with plasma exchanges ($n = 18$), 7 with plasma exchanges, 4 with rituximab, and 3 with vincristine. Twenty-three patients (55%) achieved a resolution of TMA (defined as schizocytes levels $< 0.3\%$, normalization of LDH levels and decrease in transfusion support) a median of 48 (range 5–165) days after diagnosis of TMA. For non-responders ($n = 19$), TMA was deemed the main cause of death in three patients who had no other life-threatening complication at that time. Primary causes of death in the remaining non-responders included infection ($n = 4$), progressive disease ($n = 3$), bleeding ($n = 3$), acute GVHD ($n = 3$), chronic GVHD ($n = 2$), and interstitial pneumonia ($n = 1$). Forty-three percent of patients without TMA versus 69% of those with TMA experienced secondary platelet failure ($P = 0.002$). One year after TMA, creatinine (12.8 ± 6.7 mg/l versus 12.9 ± 4.3 mg/l, $P = 0.9$) and platelet ($195 \pm 91 \times 10^9$/l versus $168 \pm 96 \times 10^9$/l, $P = 0.4$) levels were similar in patients without or with antecedent TMA. One-year survival from diagnosis of TMA was 20%. By comparison, the 1-year survival from

Table 2 Clinical factors for prediction of TMA

Variable	*No. of patients (n = 287)*	*No. of patients with TMA (%) (n = 42)*	P-*value*
Patient gender			
Male	184	24 (13)	
Female	103	18 (17)	0.3841
Patient age (continuous variable)	—	—	0.59
Donor			
HLA-identical sibling	114	8 (7)	
6/6 HLA antigen-matched unrelated	151	30 (20)	
HLA-mismatched	22	4 (18)	0.0121
Conditioning regimen			
Nonmyeloablative	176	25 (14)	
High dose	111	17 (15)	0.8642
Immunosuppression			
CD34/CD133 + CSP	56	6 (11)	
CSP	10	0 (0)	
CSP + MTX	35	9 (26)	
CSP + MTX + ATG	7	0 (0)	
MMF + CSP/Tacro	179	27 (15)	0.1322
Acute GVHD			
Grade 0–1	188	20 (11)	
Grade 2	58	5 (9)	
Grade 3–4	41	17 (41)	< 0.0001
CMV infection			
No	156	20 (13)	
Yes	131	22 (17)	0.4027
CMV disease			
No	252	33 (13)	
Yes	35	9 (25)	0.0698
Invasive aspergillosis			
No	250	36 (14)	
Yes	37	6 (16)	0.8032
Prior HCT			
No	180	26 (14%)	
Yes	107	16 (15%)	1.0
Tacrolimus as GVHD prophylaxis			
No	200	31 (15.5)	
Yes	87	11 (12.6)	0.59
Sirolimus administration			
No	277	40 (14)	
Yes	10	2 (20)	0.6442

Abbreviations: ATG = anti-thymocyte globulin; CSP = cyclosporine; HCT = hematopoietic cell transplantation; MMF = mycophenolate mofetil; Tacro = tacrolimus; TMA = thrombotic microangiopathy; URD = unrelated donor.

Table 3 Clinical factors predicting for TMA in a multivariate Cox model

	Hazard ratio (95% CI)	P-*value*
Grade 3–4 acute graft-versus-host disease	2.3 (1.5–3.5)	<0.0001
Nonmyeloablative versus high-dose conditioning	0.56 (0.36–0.88)	0.0121
Major ABO mismatch	0.76 (0.52–1.11)	0.15
Minor ABO mismatch	1.2 (0.9–1.8)	0.25
Unrelated donor	1.6 (1.1–2.2)	0.014
1/6 HLA-antigen mismatch	1.1 (0.6–2.0)	0.78
Patient age[a]	1.01 (1.00–1.03)	0.045
Prior HCT	0.82 (0.56–1.2)	0.33
Tacrolimus or cyclosporine as GVHD prophylaxis	0.73 (0.47–1.1)	0.16
Sirolimus administration	0.8 (0.36–1.8)	0.59

Abbreviations: HCT = hematopoietic cell transplantation; TMA = thrombotic microangiopathy.
[a]Modeled as a continuous linear variable.

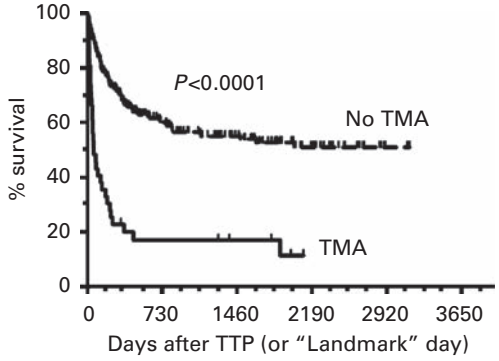

Figure 1 Semi-landmark plots illustrating impact of TMA on overall survival.

day 52 in patients who did not experience TMA and were alive on day 52 (pseudo-landmark analysis[7]) was 67% ($P<0.0001$, Figure 1). As expected, median survival from TMA diagnosis was higher in patients who achieved resolution of TMA compared with those who did not (median 218 days versus 27 days, $P<0.001$). Further, 1-year survival was significantly worse in patients requiring platelet transfusions after TMA (9%) versus in those who did not (56%, $P=0.006$). Finally, 100-day and 1-year overall survivals from diagnosis of TMA were 40 and 18%, respectively, in nonmyeloablative recipients versus 41 and 24%, respectively, in high-dose recipients ($P=0.8$).

Discussion

TMA is a well-known complication of allogeneic HCT.[1,2] The relative roles of the conditioning regimen and alloreactivity in post-transplant TMA have not been completely elucidated. The primary objective of the current retrospective study was to compare TMA incidence in patients given nonmyeloablative versus high-dose conditioning. Other objectives included determining factors predicting for TMA, and analyzing the impact of TMA occurrence on OS. Several observations have been made.

First, the incidence of TMA was lower in the nonmyeloablative than in the high-dose setting in the multivariate Cox analysis, suggesting that conditioning intensity might have a role in the physiopathology of post-transplant TMA. Two recent studies compared the incidence of TMA after myeloablative or after 'reduced-intensity' conditioning and failed to show significant differences.[14,15] This might be due to the fact that the 'reduced-intensity' conditioning regimen (combining relatively high doses of fludarabine and busulfan 8 mg/kg) used in these studies was still relatively intense and capable of inducing endothelial damage. In support to this hypothesis, sinusoidal obstructive syndrome has been observed with this conditioning regimen, when never in our patients undergoing nonmyeloablative conditioning. For these reasons, we chose to classify the four patients given grafts after fludarabine and busulfan 8 mg/kg in this study within the 'high-dose' chemotherapy group.

Second, our study showed that severe acute GVHD and unrelated donor were two strong predictors of TMA occurrence, in agreement with several earlier reports.[15–20] The association between acute GVHD and TMA was not surprising given that endothelial cells are the targets of graft-versus-host reactions.[21] The association between unrelated donor and TMA might be explained by the wider antigenic disparity between donors and recipients in the setting of unrelated donor transplantation, increasing the risk of host endothelial injury by donor immune cells. In contrast, our study failed to show significant associations between infections and post-transplant TMA as observed in some earlier reports.[17,18] The lack of association between infection and TMA in this study might be due to the relatively low number of patients included.

Third, patients who experienced TMA had a dramatically lower probability of survival than those who did not experience this complication. TMA was the primary cause of death of 7% of patients with TMA, and a secondary cause of death in 24%. The poor outcome in patients with TMA could also be related to the strong associations observed between TMA and severe GVHD, which is one of the leading causes of nonrelapse mortality after allogeneic HCT.[4,5,7] Supporting this hypothesis, 26% of patients with non-responding TMA died of GVHD in this study.

We should acknowledge that comparisons of TMA incidence between different groups of investigators might be difficult because of the relatively non-specific criteria for diagnosis of TMA and variable sensitivity to the diagnosis in different institutions. This probably explains the large range of TMA occurrence reported in different studies (from 0.5 to 63%).[22] However, the incidence of TMA observed in our high-dose chemotherapy cohort (15% at 1-year) is well in the range of what has been reported recently by other groups of investigators (10–20%),[14,15,23] one of them using a similar definition for TMA (18%).[15]

In summary, our data suggest that though severe acute GVHD and unrelated donor are strong predictors for TMA occurrence, patients undergoing nonmyeloablative conditioning might have a slightly lower risk of TMA than those given high-dose conditioning.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We are grateful to physicians, physicians' assistants, and clinical staff for their dedicated care of the patients. FB is a senior research associate and YB a research director of the National Fund for Scientific Research (FRS-FNRS), Belgium. The study was in part supported by funds from the FNRS, the anti-Cancer Center from the University of Liège, and by the Belgian Federation against Cancer (FBC).

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