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Blood and Marrow Transplant Clinical Trials Network Toxicity Committee Consensus Summary: Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation

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ABSTRACT

The syndrome of microangiopathic hemolysis associated with renal failure, neurologic impairment, or both is a recognized complication of hematopoietic stem cell transplantation. This entity is often called hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP), yet it is clear that the pathophysiology of transplant-associated HUS/TTP is different from that of classic HUS or TTP. Furthermore, the incidence of this syndrome varies from 0.5% to 76% in different transplant series, primarily because of the lack of a uniform definition. The toxicity committee of the Blood and Marrow Transplant Clinical Trials Network has reviewed the current literature on transplant-related HUS/TTP and recommends that it be henceforth renamed posttransplantation thrombotic microangiopathy (TMA). An operational definition for TMA based on the presence of microangiopathic hemolysis and renal and/or neurologic dysfunction is proposed. The primary intervention after diagnosis of TMA should be withdrawal of calcineurin inhibitors. Plasma exchange, although frequently used in this condition, has not been proven to be effective. In the absence of definitive trials, plasma exchange cannot be considered a standard of care for TMA. It is hoped that these positions will improve the identification and reporting of this devastating complication after hematopoietic stem cell transplantation and facilitate future clinical studies for its prevention and treatment.

KEY WORDS

Hemolytic uremic syndrome • Thrombotic thrombocytopenic purpura • Microangiopathy • Anemia • Thrombocytopenia • Stem cell transport

INTRODUCTION

Thrombotic microangiopathy (TMA) syndromes, presenting as hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP), are well-recognized complications of hematopoietic stem cell transplantation (HSCT). The reported incidence of TMA after allogeneic HSCT varies from 0.5% to 76% [1-5]. In a recent literature review including 35 published articles involving more than 5423 allogeneic HSCT recipients, George et al. [6] identified 447 (8.2%) cases of posttransplantation TMA, with a median mortality of 75% within 3 months of the diagnosis. The large variability in published incidence arises from the fact that there are no uniformly accepted diagnostic criteria for this clinical syndrome. Because patients after HSCT often develop anemia, thrombocytopenia, fever, renal dysfunction, and fragmented red blood cells (RBCs) from many competing causes, a diagnosis of TMA in this population is often

very difficult to establish and requires a high index of clinical suspicion. However, agreement on diagnostic criteria will be crucial to accurately assess the effects of new agents (eg, new calcineurin inhibitors) on the incidence of this disorder and to study interventions for its prevention or treatment.

In an effort to establish guidelines for reporting adverse events after HSCT in clinical trials facilitated by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), the BMT CTN Committee on Transplant Toxicity convened to review the current knowledge about TMA as a transplantation complication and to propose an operational definition for this clinical syndrome.

CLINICAL FEATURES

The classic presentation of TMA is the relatively acute onset of anemia and thrombocytopenia with evidence of RBC fragmentation in the peripheral blood smear. An associated increase in the serum lactic dehydrogenase (LDH), with concomitant acute renal dysfunction, occurs in the large majority of patients. Neurologic deficits, including but not restricted to confusion and seizures, occur in up to half the cases in some series. The clinical spectrum of TMA is broad and can range from life-threatening neurologic or renal complications requiring plasma exchange, dialysis, or both to asymptomatic anemia with schistocytosis and mild renal dysfunction. The onset of posttransplantation TMA usually occurs within the first 100 days after stem cell infusion. In a reported series from the European Blood and Marrow Transplant Group, the median onset was 44 days after HSCT, with a range of 13 to 319 days [4]. Clinical hemorrhage, graft-versus-host disease (GVHD), and infections were common causes of death in this population. Several reports have suggested that infections from aspergillus or viruses such as cytomegalovirus, adenovirus, human herpesvirus 6, and parvovirus B19 can in themselves lead to microangiopathic hemolysis and therefore mimic the diagnosis of TMA [7-14].

In HSCT series, severe TMA is variably associated with advanced recipient age, female sex, unrelated or HLA-mismatched donor grafts, GVHD, viral or fungal infections, and use of calcineurin inhibitors such as cyclosporine [1-5]. Investigators at the Dana-Farber Cancer Institute have also reported an increased risk for TMA in patients who receive sirolimus with tacrolimus as GVHD prophylaxis [15].

DEFINITION OF TMA

The committee proposes that the term *posttransplantation TMA* should be used to describe HUS and TTP associated with stem cell transplantation, because available data indicate an etiology and natural history different from those with HUS/TTP outside the HSCT setting. The participants agree that it is important to have a uniform operational definition for TMA so that future descriptive or interventional studies can incorporate comparably defined patient populations. Current criteria used to define TMA in the literature are highly varied and confusing. For example, in the literature review of HUS/TTP after HSCT published by George et al. [6], 28 sets of diagnostic criteria were used in the 35 articles included in the review. Among these articles, the most frequently cited diagnostic features, in descending frequency, were (1) RBC fragmentation, (2) increased serum LDH, (3) decreased platelet count, (4) renal failure, and (5) neurologic dysfunction. Less commonly included criteria were negative tests for disseminated intravascular coagulation and negative Coombs test results. The last 2 features were included in the reports published from the European Blood and Marrow Transplant Group and Gruppo Italiano Trapianto Midollo Osseo [3,4]. The committee also reviewed the definition used in a recent retrospective analysis of TMA among patients receiving tacrolimus and sirolimus conducted by Henry et al. [15] at the Dana-Farber Cancer Institute.

After consideration of these data, the committee proposes the following operational definition of TMA for validation in future prospective trials (Table 1): (1) RBC fragmentation with ≥2 schistocytes per high-power field on peripheral smear; (2) concurrent increased serum LDH above institutional baseline; (3) concurrent renal and/or neurologic dysfunction without other explanations, where renal dysfunction is defined as either a doubling of serum creatinine from baseline, where baseline is the creatinine taken before hydration and just before initiation of the conditioning regimen, or a 50% decrease in creatinine clearance from baseline; and (4) negative direct and indirect Coombs test results. The panel decided against using thrombocytopenia as a diagnostic criterion because transplant recipients often have low platelet counts from various causes during the early posttransplantation period.

Table 1. *BMT CTN Toxicity Committee Consensus Definition for TMA*

1. **RBC fragmentation and ≥2 schistocytes per high-power field on peripheral smear**
2. **Concurrent increased serum LDH above institutional baseline**
3. **Concurrent renal* and/or neurologic dysfunction without other explanations**
4. **Negative direct and indirect Coombs test results**

*Doubling of serum creatinine from baseline (baseline = creatinine before hydration and conditioning) or 50% decrease in creatinine clearance from baseline.

STAGING OF TMA

Pettitt and Clark [1] previously proposed classifying posttransplantation TMA into 4 distinct but overlapping subtypes based on clinical features and the severity of the clinical course: (1) multifactorial fulminant TMA, (2) conditioning-associated HUS, (3) cyclosporine-associated nephrotoxicity with microangiopathic hemolysis, and (4) cyclosporine-associated neurotoxicity with microangiopathic hemolysis. However, subcategorization of TMA cases into these subtypes is difficult because of overlapping features in many cases. For example, according to this classification scheme, patients with cyclosporine-associated nephrotoxicity or neurotoxicity with microangiopathic hemolysis would have clinical features similar to those with multifactorial fulminant TMA, except for the severity of the clinical outcome. Consequently, this classification does not seem to be a useful system for prospectively staging patients with developing TMA.

Zeigler et al. [2] proposed using a TTP index as a method of scoring clinical severity. The TTP index represents the ratio of serum LDH to platelet count at diagnosis; a ratio of ≥20 indicates severe TTP. However, this system is subject to variability from differing institutional normal laboratory values for serum LDH and also from the fact that platelet counts are often reduced for reasons other than TTP in the posttransplantation patient population. Uderzo et al. [16] applied the TTP index in their retrospective series of 28 cases of pediatric posttransplantation TTP. They found that peak serum LDH, but not the TTP index at diagnosis, was significantly associated with mortality.

The committee concluded that there are currently insufficient data to endorse a staging/grading system specific for posttransplantation TMA. Instead, the participants suggest that the severity of TMA after HSCT should be assessed according to the current National Cancer Institute Common Toxicity Criteria adverse event grading system, as shown in Table 2. However, the committee agrees that a minor modification to this system is necessary to render it consistent with the currently proposed operational definition. Specifically, patients with Common Toxicity Criteria grade 1 will not meet the currently proposed definition for TMA because they do not have renal or neurologic dysfunction. The committee believes that this exclusion is justifiable because some schistocytosis is common after HSCT and that this isolated finding without associated organ dysfunction is likely to have little clinical significance. On the basis of these considerations, only Common Toxicity Criteria severity grades 2 to 4 should be applicable in reporting TMA.

Table 2. *Common Toxicity Criteria for BMT Thrombotic Microangiopathy*

Grade 1	**Evidence of RBC destruction (schistocytosis) without clinical consequences**
Grade 2	**Evidence of RBC destruction with increased creatinine ≤3 times the ULN**
Grade 3	**Evidence of RBC destruction with creatinine >3 times the ULN not requiring dialysis**
Grade 4	**Evidence of RBC destruction with renal failure requiring dialysis, and/or encephalopathy**

ULN indicates upper limit of normal.

Table 3. *Response and Mortality for Post-HSCT TMA Treated with Plasma Exchange (PE)*

Study	No. Treated with PE	Response	Mortality
Silva et al. [17]	8	4 (50%)	7 (88%)
Sarode et al. [18]	8	3 (38%)	6 (75%)
Dua et al. [19]	16	8 (50)%	12 (80%)
Llamas et al. [20]	10	8 (80%)	7 (70%)
Paquette et al. [21]	7	0 (0%)	7 (100%)
Iacopino et al. [3]	6	1 (17%)	5 (83%)
Uderzo et al. [16]	16 (pediatric)	NA	7 (44%)
Roy et al. [22]	17	3 (18%)	16 (94%)
Fuge et al. [5]	17	6 (35%)	16 (94%)
Ruutu et al. [4]	5	4 (75%)	4 (80%)
Sarkodee-Adoo et al. [23]	11	2 (18%)	9 (82%)

NA indicates not available.

THERAPY FOR POSTTRANSPLANTATION TMA

There was consensus that calcineurin inhibitors should be discontinued after diagnosis of posttransplantation TMA, but there are currently insufficient data to recommend other specific therapies. Available data regarding plasma exchange for treatment of posttransplantation TMA indicate poor results compared with those observed with de novo TTP. Although there are anecdotal reports of patients who seem to respond to plasma exchange, randomized controlled studies are lacking, and the efficacy of this treatment has not been clearly borne out in the literature. As shown in Table 3, which lists published series containing 5 or more patients with posttransplantation TMA treated with plasma exchange, response rates are generally less than 50%, and mortality rates among patients treated with this modality remain greater than 80%. The committee acknowledges that the high mortality rates in these series may be skewed by selection bias because only the sickest patients are likely to receive the treatment. For this reason, determination of any survival benefit attributable to plasma exchange in the absence of a controlled study is impossible. Given the limited available literature, the committee believes that the universal use of plasma exchange for posttransplantation TMA cannot be currently considered the standard of care. The committee agrees that it would be reasonable to substitute corticosteroids or other immune-suppressive agents to pre-

vent GVHD as calcineurin inhibitors are discontinued. Whether corticosteroids have benefits in treating TMA is unknown.

CONCLUSIONS

TMA is an underrecognized but potentially devastating complication of allogeneic HSCT. We propose uniform diagnostic criteria to monitor this complication in all BMT CTN trials. These include RBC fragmentation, increased LDH, concurrent renal and/or neurologic dysfunction (without other explanations), and negative direct and indirect Coombs test results. In the absence of definitive trials, we recommend that plasma exchange not be considered a standard of care for TMA. These recommendations are intended to facilitate the identification and reporting of this difficult complication after HSCT and to facilitate future clinical studies for its prevention and treatment.

APPENDIX

The BMT CTN was established in October 2001 with the primary mission of conducting large multiinstitutional clinical trials to advance the field of hematopoietic stem cell transplantation. It is a network composed of a core of 16 clinical medical centers that perform stem cell transplantation across North America and is funded by the National Heart, Lung and Blood Institute and National Cancer Institute divisions of the U.S. National Institutes of Health. The Data Coordination Center, which coordinates data collection and facilitates the administrative activities of the CTN, is composed of the International Bone Marrow Transplantation Registry/Autologous Bone & Marrow Transplant Registry, National Marrow Donor Program, and EMMES Corporation. The toxicity committee of the BMT CTN is composed of a panel of Data Coordination Center representatives and transplant physicians from core medical institutions of the CTN. The toxicity committee convenes on a regular basis to review clinical trials conducted through the CTN and provides guidelines for facilitating the identification and reporting of transplant toxicity that occurs on these trials. Additional information on the BMT CTN may be found on the BMT CTN Web site at http://www.bmtctn.net.

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