Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group

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ABSTRACT

Background and Objectives

There are no widely accepted criteria for the definition of hematopoietic stem cell transplant -associated microangiopathy (TAM). An International Working Group was formed to develop a consensus formulation of criteria for diagnosing clinically significant TAM.

Design and Methods

The participants proposed a list of candidate criteria, selected those considered necessary, and ranked those considered optional to identify a core set of criteria. Three obligatory criteria and four optional criteria that ranked highest formed a core set. In an appropriateness panel process, the participants scored the diagnosis of 16 patient profiles as appropriate or not appropriate for TAM. Using the experts' ratings on the patient profiles as a gold standard, the sensitivity and specificity of 24 candidate definitions of the disorder developed from the core set of criteria were evaluated. A nominal group technique was used to facilitate consensus formation. The definition of TAM with the highest score formed the final proposal.

Results

The Working Group proposes that the diagnosis of TAM requires fulfilment of all of the following criteria: (i) >4% schistocytes in blood; (ii) *de novo*, prolonged or progressive thrombocytopenia (platelet count $<50x10^9$/L or 50% or greater reduction from previous counts); (iii) sudden and persistent increase in lactate dehydrogenase concentration; (iv) decrease in hemoglobin concentration or increased transfusion requirement; and (v) decrease in serum haptoglobin. The sensitivity and specificity of this definition exceed 80%.

Interpretation and Conclusions

The Working Group recommends that the presented criteria of TAM be adopted in clinical use, especially in scientific trials.

Key words: bone marrow transplantation, hematopoietic stem cell transplantation, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, transplant-associated microangiopathy.

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Microangiopathy following hematopoietic stem cell transplantation, particularly allogeneic transplantation, is a well recognized but poorly defined syndrome. A number of terms have been used to describe this entity, including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), TTP-HUS, thrombotic microangiopathy, transplant-associated microangiopathy (TAM), and microangiopathic hemolytic anemia. The pathogenesis is not well understood; endothelial toxicity caused by chemoradiotherapy, infections, immunosuppressive drugs, and graft-versus-host disease have been thought to play a role.[1-3] In published reports, an association has been variably found between this disorder and female sex,[4-6,8] an unrelated donor,[5,7-9] presence of graft-versus-host disease,[1,4,6,8,9] fungal or viral infections,[8,9] and administration of cyclosporine A[1] or sirolimus.[10] The onset of TAM usually occurs within 150 days post-transplantation.[4,5,11] Despite some features in common, TAM differs from *de novo* TTP in many aspects including the absence of severe ADAMTS13 deficiency, a different spectrum of clinical symptoms, poor response to plasmapheresis, and the lack of evidence of systemic microthrombus formation.[12]

Minor laboratory findings suggestive of microangiopathy are seen in a large proportion of allogeneic transplant recipients.[1,13-15] The reported proportions of patients developing a clinically significant microangiopathy syndrome have varied greatly. Recently George and co-workers[12] presented a review of published reports on microangiopathy following allogeneic stem cell transplantation. Twenty-eight different definitions of this syndrome had been used in the 35 reviewed reports. Nineteen different parameters had been used as criteria, many of them indicating the same factors phrased differently. The most commonly used criteria were red cell fragmentation, increased lactate dehydrogenase (LDH) concentration, a decrease in platelet count or increased platelet transfusion requirement, renal failure, decreased hemoglobin level or increased red blood cell transfusion requirement, a neurological abnormality, the absence of disseminated intravascular coagulation, and a negative direct antiglobulin test. Reflecting the different definitions, the incidence of post-transplant microangiopathy varied in the reports from 0.5 to 63.6%, the median frequency of diagnosis being 7.9%. The mortality in the different series ranged from 0 to 100 %; the overall mortality rate was 61%. Of the deceased patients, 82% died within 3 months.

The lack of accepted standard criteria and the marked heterogeneity in the definitions used largely prevent meaningful comparisons of the published reports. For clinical studies, particularly those aiming at the development of prevention and treatment of TAM, a widely accepted definition of this complication would be highly desirable. On an initiative of the European Group for Blood and Marrow Transplantation (EBMT) and the European LeukemiaNet, an International Working Group was formed with the intention to produce, by a consensus process, a proposed definition of the clinical syndrome of transplant-associated microangiopathy. The purpose was to identify rigorous, consistent, and feasible criteria applicable both to future clinical trials and also to routine practice.

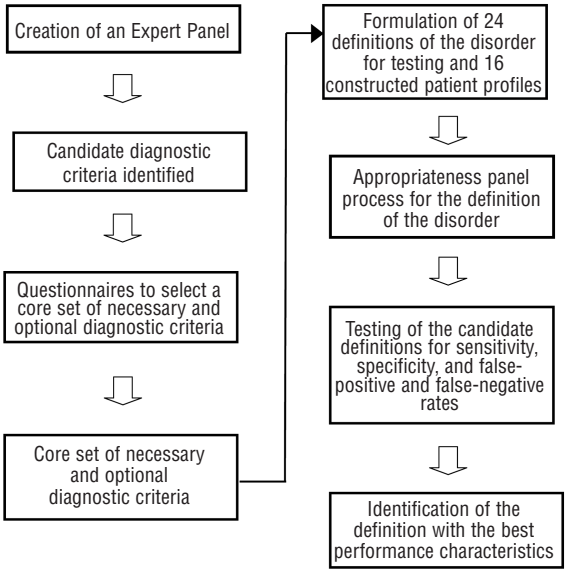

Figure 1. Process of choosing the core set of diagnostic criteria and, using the core set, a definition of TAM.

Design and Methods

The diagnostic criteria for TAM were developed by a multistep process, based on the approach of the American College of Physicians[16] with some modifications. This process is described below and summarized in Figure 1. An Expert Panel, constituted in September 2004, was composed of 14 experts in microangiopathic disorders and/or clinical stem cell transplantation (members of the Working Group) and was chaired by a clinician with expertise in clinical epidemiology (GB). After the initial meetings, the Expert Panel agreed on the aim of the project to develop diagnostic criteria for clinically significant TAM.

Development of a core set of criteria for the diagnosis of TAM

A questionnaire was mailed to each member of the Expert Panel asking them to propose candidate diagnostic criteria, and these criteria were further refined in a Delphi process[17] with a second questionnaire that asked the panelists to rank the top choices among the candidate criteria. An *other* category was provided for criteria not included in

the preliminary list. All the questionnaires were returned, and the candidate criteria were ranked according to their priority votes, with the 12 criteria that ranked highest forming the preliminary core set of criteria. A third questionnaire was mailed to each Panel member asking them to select the *necessary* criteria, defined as criteria that must be present and the presence of which must be ascertained in order to define patients as having TAM. All the questionnaires were returned, three necessary criteria were identified (>80 % consensus) and the other candidate criteria were ranked according to their priority votes. The three necessary criteria and the four optional criteria that ranked highest formed the *core set* of criteria.

Development of candidate diagnostic definitions

Using a mail-only system, we performed an appropriateness panel process in order to develop candidate diagnostic definitions of TAM. The overall goal of the process was to decide upon the definition of the disorder based on the core set of criteria, using a combination of statistical and consensus formation techniques.[18] In order to achieve this, the co-ordinator of the project generated 16 constructed patient profiles based on the core set of diagnostic criteria. The profiles listed the findings of the patients for each criterion of the core set. The participants were asked to rate each of the profiles as *appropriate* or *not appropriate* for the diagnosis of TAM based on the individual physician's clinical judgement. If an 80% consensus about whether a constructed patient's profile did or did not have TAM was not achieved, the case with the comments from the panelists was redistributed to the panelists, and a second vote was taken. If an 80% consensus was still not attained, the patient's profile was declared uninterpretable and was not considered further.

By using combinations of the variables in the core set, 24 sound candidate definitions of TAM were generated for testing. The candidate definitions required the presence of the three necessary criteria and one to four optional criteria.

Evaluation of the performance characteristics of the candidate diagnostic definitions

The 16 profiles were then used to test the candidate diagnostic definitions for their ability to classify individual patients as having or not having TAM, using the physicians' consensus in the rating of the constructed patient profiles as a gold standard. The agreement between the decision based on the criteria and the consensus of the physicians was assessed. Only the patient profiles for which a physician consensus was achieved were used. For each definition, we calculated the sensitivity (ability of the definition to identify a patient as having TAM when he/she had been classified as having TAM by the physicians), the specificity (ability of the definition to identify a patient as not having TAM when he/she had been classified as not having TAM by the physicians), the rate of false-positivity ([number of patients falsely identified as having TAM by the given criteria divided by all patients identified as having TAM×100), and the rate of false-negativity ([number of patients falsely identified as not having TAM by the given criteria divided by all patients identified as not having TAM] ×100). We used the kappa statistic[19] as an additional measure of agreement between the evaluation made by the physicians and the definitions: κ values ≥0.7 were considered to be evidence of agreement.

At a final consensus questionnaire, the Panel ranked the top three candidate definitions based on face validity and content validity, and the definition that obtained the highest ranking was selected as the first choice.

Table 1. Ranking of candidate criteria.

N.	Diagnostic criterion	Sum of ranks
1	RBC fragmentation	323
2	*De novo*, prolonged or progressive thrombocytopenia	301
3	Sudden and persistent increase in LDH	283
4	Hb decrease or increased RBC transfusion requirement	252
5	Sudden and persistent increase in BUN or creatinine	240
6	Direct antiglobulin test negative	235
7	Refractoriness to platelet transfusions	222
8	Neurologic abnormality	218
9	Decreased haptoglobin	199
10	Reticulocyte increase	178
11	Exclusion of disseminated intravascular coagulation	161
12	Exclusion of high levels of cyclosporine A	153
13	Increased free hemoglobin	146
14	Exclusion of veno-occlusive disease	142
15	Exclusion of aspergillosis	141
16	Exclusion of graft-versus-host disease	139
17	ADAMTS13 decreased or absent	137
18	Renal pathology demonstrating thrombotic microangiopathy	136
19	Decrease of the large fraction of vWF-multimeric pattern	132
20	Exclusion of disease relapse	122
21	Exclusion of active cytomegalovirus disease	111
22	Exclusion of adenovirus	108
23	Exclusion of collagen vascular disease	102
24	Exclusion of malignant hypertension	100
25	Exclusion of human herpes virus 6	90
26	Refractoriness to plasma exchange/FFP replacement	87
27	Exclusion of parvovirus B19	81

Each member of the Panel ranked the 27 criteria assigning number 27 to the most important measure and 1 to the least important one using each rank only once. FFP: fresh-frozen plasma.

Results

The Expert Panel listed 27 criteria (15 positive, i.e. the presence of which indicates TAM, and 12 negative, i.e. the presence of which excludes TAM), to be included as candidate criteria for the diagnosis of TAM (Table 1). The three criteria with the highest preference rate (>80% consensus) as being necessary for the diagnosis were: (i) increased percentage (>4%) of schistocytes in

Table 2. Final results for the three best definitions of TAM. Each definition consists of three *necessary* criteria and, in addition, other criteria as indicated.

Definition	*Sensitivity*	*Specificity*	*False-positive rate*	*False-negative rate*
The three necessary criteria (i-iii) **plus** (iv) decrease in hemoglobin concentration or increased red blood cell transfusion requirement **and** (v) decrease in serum haptoglobin	1	1	0	0
The three necessary criteria (i-iii) **plus** (iv) decrease in hemoglobin concentration or increased red blood cell transfusion requirement **and** (v) at least **one** of the following: a. decrease in serum haptoglobin b. sudden and persistent increase in BUN or creatinine c. neurological symptoms	1	0.75	0.43	0
The three necessary criteria (i-iii) **plus** (iv) at least **two** of the following: a. decrease in hemoglobin concentration or increased red blood cell transfusion requirement b. decrease in serum haptoglobin c. sudden and persistent increase in BUN or creatinine d. neurological symptoms	1	0.41	0.63	0

"Necessary" criteria: (i) increased percentage (>4%) of schistocytes in peripheral blood; (ii) de novo, prolonged or progressive thrombocytopenia (platelet count less than 50×10⁹/L or a 50% or greater decrease from previous counts); (iii) sudden and persistent increase in LDH.

peripheral blood; (ii) *de novo*, prolonged or progressive thrombocytopenia (platelet count less than 50×10⁹/L or a 50 % or greater decrease from previous counts); and (iii) sudden and persistent increase in LDH. These criteria were regarded as necessary. When the other criteria were ranked according to their priority score, the four with the highest rank for the core set were the following: (i) a decrease of hemoglobin concentration or increased red cell transfusion need; (ii) a sudden and persistent increase in BUN or creatinine; (iii) neurologic abnormalities; (iv) decreased haptoglobin.

Using the appropriateness panel process, the 14 Panel members scored eight of the 16 patients' profiles as having TAM, and eight as not having TAM. Three of the 24 definitions of TAM showed a sensitivity >80%. These three definitions, their corresponding sensitivity and specificity and false-positive and false-negative rates are shown in Table 2. Face validity, i.e. a subjective judgment of clinical appropriateness, and content validity, i.e. a subjective judgment of the relevance of the definition, were analyzed and discussed by the Panel. Taking into account the statistical performance of the definition and the validity judgments, the final definition of TAM was as follows (Table 3): all of the following present: (i) increased percentage (>4%) of schistocytes in peripheral blood; (ii) *de novo*, prolonged or progressive thrombocytopenia (platelet count less than 50×10⁹/L or a 50% or greater decrease from previous counts); (iii) sudden and persistent increase in LDH; (iv) a decrease in hemoglobin or increased red blood cell transfusion requirement, and (v) a decrease in serum haptoglobin.

Table 3. The definition of transplant-associated microangiopathy (TAM) by the International Working Group.

All of the following present

- Increased percentage (>4%) of schistocytes in peripheral blood
- *De novo*, prolonged or progressive thrombocytopenia (platelet count less than 50x10⁹/L or a 50% or greater decrease from previous counts)
- Sudden and persistent increase in LDH
- Decrease in hemoglobin concentration or increased red blood cell transfusion requirement
- Decrease in serum haptoglobin concentration

Discussion

In this work we report the results of a consensus process on the diagnostic definition of TAM. In the absence of a specific biological marker for the disorder, we were aware that searching for a definition of TAM raised both a true diagnostic issue, i.e. what are the diagnostic criteria and how to use them for the diagnosis, and a classificatory one, i.e. how to distinguish this disorder among a spectrum of disorders with similar features. To focus the problem, the Working Group stated that the aim of this project was to arrive at a definition of clinically significant TAM to be primarily used in clinical trials. The task of finding a consensus for diagnostic criteria was complicated by the fact that the area is characterized by reports which do not deal with prospective clinical trials, and few *ad hoc* studies report the statistical information needed for summing up the evidence. The conceptual framework of this project was an assumption that acknowledged experts have an implicit and comprehensive mastery of the scientific and practical information that would yield the most appropriate definition. The value of this type of consensus approach to the definition of operational criteria in medicine has been exploited in many similar processes.[20,21]

Using consensus formation and a statistical approach, the results of this project suggest that TAM can be defined with five criteria: increased percentage of schistocytes, thrombocytopenia, increased LDH, a decrease in hemoglobin concentration or increased transfusion requirement, and a decrease in serum haptoglobin, as specified in Table 3. This definition is constructed from criteria widely used in different definitions of post-

transplant microangiopathy, but not in this precise combination. The results of this work were derived from a structured consensus process and a statistical analysis of the reactions of the experts to 16 constructed patient profiles. The characteristics of the resulting definition of the disorder, i.e. its specificity and sensitivity, should be interpreted as a result of uncertainty inherent both to the consensus process and the idea the panelists had of the disorder. The former depends on the size of the expert panel and the number of cases used during the consensus process; the latter reflects the absence of clear markers for defining the disorder. The resulting definition had a 100% specificity and a 100% sensitivity, thus producing no false positive and no false negative definitions. Therefore these criteria seem to be appropriate when used for enrolling patients into clinical trials.

The Working Group chose to use the term *transplant-associated microangiopathy* for the disorder. This is a descriptive term not referring to the pathogenesis which is unclear and probably heterogeneous. The Working Group wanted to avoid the word *thrombotic*, as systemic microthrombus formation has not been shown to play an essential role in this complication, contrary to *de novo* TTP.[12] This terminology may also be helpful in pointing out the difference in the utility of plasmapheresis in the treatment of TTP and TAM.

The present criteria for TAM were developed for practical clinical purposes, especially for clinical trials, and the definition has limitations. It does not take into account the etiology of the microangiopathic process. The definition has not been prospectively validated in patients; this remains to be done in future trials. The criteria are not independent from each other, they are essentially different markers of microangiopathic hemolytic anemia and, in addition, consumption thrombocytopenia. However, as allogeneic transplant patients often have multiple problems that may affect one or more of the individual criteria, the presented combination of criteria confirms the microangiopathic red cell destruction. The defined level for the proportion of schistocytes is only an estimate, and it cannot be concluded that patients with a somewhat lower or higher schistocyte level would have a different outcome. Nevertheless, in the present state of great heterogeneity in the definitions used, a consensus definition by a relatively large group of experts is of value in an effort to standardize the definition of TAM for clinical trials.

The treatment of TAM is problematic, and no consistently effective therapies are available. The subject was recently reviewed by George *et al*.[12] On purpose, this consensus panel did not address the topic of treatment.

During the present consensus process the Toxicity Committee of the Blood and Marrow Transplant Clinical Trials Network published a consensus summary of thrombotic microangiopathy after hematopoietic stem cell transplantation.[22] They presented a consensus definition for this complication which differs markedly from the present proposal. Their definition included the presence of schistocytes, increased LDH level, concurrent renal and/or neurological dysfunction, and a negative Coombs' test. They did not include thrombocytopenia among the criteria because transplant recipients often have low platelet counts from various causes during the early post-transplantation period. The present Expert Panel concluded that although the causes of thrombocytopenia may be variable in this group of patients, low or decreasing platelet counts are an essential feature of TAM, and a patient with a stable normal platelet count would be unlikely to have TAM. *De novo*, prolonged or progressive thrombocytopenia ranked second highest as a criterion for TAM in the consensus process. Nephropathy and neurological abnormalities were among the highest ranked optional criteria but they did not qualify for the final set of criteria. Renal problems are very common in allogeneic transplant recipients but the causes are manifold, including the effects of cyclosporine, and a proportion of patients with TAM do not have nephropathy.[4,5] Neurological abnormalities are a less prominent feature in TAM than in *de novo* TTP.[4,5] The Expert Panel also considered the role of exclusion criteria such as a positive Coombs' test and the presence of signs of disseminated intravascular coagulation but their ranking in the consensus process did not indicate their inclusion in the final set of criteria.

In conclusion, the Working Group proposes that the presented criteria for transplant-associated microangiopathy, which were developed using an American College of Physicians-based consensus process and offer a definition with more than >80% sensitivity and specificity, be adopted for clinical use, especially for scientific trials.

Author Contributions

All authors participated in the consensus process. TR and GB wrote the manuscript. GB chaired the Expert Panel and was in charge of the statistics. All authors participated in the formulation of the report and accepted the final manuscript. The authors would like to thank Monia Marchetti for her advice concerning the methodology used in this project.

Conflict of Interest

The authors reported no potential conflicts of interest.

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