Response to "Predictors of survival in thrombotic thrombocytopenic purpura" Haematologica 2013;98(5):e58

The French TMA Reference Center recently described in this Journal a predictive model for death in patients with idiopathic acquired thrombotic thrombocytopenic purpura (TTP).[1] In their paper, Chaturvedi and Bhatia claimed that our model may not be applicable to the majority of patients with TTP because we only considered patients with severe ADAMTS13 deficiency.[2] These authors suggest that all patients with an apparent diagnosis of idiopathic or secondary TTP should have been analyzed, irrespective of ADAMTS13 activity. We disagree with this view. Indeed, the association of a microangiopathic hemolytic anemia with peripheral thrombocytopenia and organ failure are not specific to TTP. Rather, these features define a heterogeneous group of disorders that have overlapping clinical manifestations and are grouped under the broader term of thrombotic microangiopathy (TMA), which includes not only TTP, but also other distinct diseases, such as the hemolytic and uremic syndrome (HUS), and TMA associated with various conditions (i.e. cancer, allogeneic hematopoietic stem cell transplantation, chemotherapy, human immunodeficiency virus infection, etc.). All these diseases have now been clearly characterized as having specific features in terms of pathophysiology, prognosis and treatment, and, therefore, cannot be considered as a single disease. TMA syndromes are currently classified on the basis of their pathophysiological mechanisms.[3,4] This new molecular classification is more adapted to the increasing use of targeted therapies, such as B-cell depleting therapies (rituximab; Mabthera®, Roche) for acquired TTP and complement blockers (eculizumab; Soliris®, Alexion) for atypical HUS.[5-7] Moreover, Chaturvedi and Bhatia wrongly consider TTP and TTP-HUS to be the same entity. The term TTP-HUS was used by some authors to group TTP and HUS together in their studies, due to the absence of explicit criteria to distinguish between the diseases on the basis of their clinical presentation and standard biology.[8] However, TTP-HUS includes distinct diseases, as reflected by the variable frequency (33-75%) of severe ADAMTS13 deficiency in this group of patients.[8-10] Conversely, 75-100% of patients diagnosed with TTP on the basis of mild renal involvement display severe ADAMTS13 deficiency, whereas most patients with severe renal failure, and considered, therefore, as having features of HUS, have detectable ADAMTS13 activity.[9,11] Likewise, the distinction of idiopathic TMA on the basis of ADAMTS13 activity (severe deficiency and detectable enzyme activity) closely matches the diagnoses of TTP and HUS, respectively.[10,12-15] Clearly, TMA can no longer be considered as a single disease in the era of molecular diagnosis and targeted therapies. Accordingly, the aim of our work was to identify original prognostic factors in a specific and homogeneous subset of patients with TMA (i.e. acquired idiopathic TTP) who were identified accurately on the basis of severe ADAMTS13 deficiency and for whom targeted therapies are available.[6] In conclusion, the comment by Chaturvedi and Bhatia revives the old issue of the crucial need for the use of a rigorous terminology in the field of TMA that is acknowledged by all national collaborative groups.[12] This requires international efforts to define consensual diagnostic criteria, treatment modalities and definitions of treatment response to allow a common language to be developed and international studies and fruitful meta-analyses to be conducted.

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