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Review

Treatment of autoimmune thrombotic thrombocytopenic purpura in the more severe forms

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ABSTRACT

Daily therapeutic plasma exchange (TPE) transformed the historically fatal prognosis of acquired, anti-ADAMTS13 antibody-mediated thrombotic thrombocytopenic purpura (TTP), leading to the current overall survival rates of >80%. However, relapses occur in up to 40% of patients and refractory disease with fatal outcomes still occurs. In this context, the introduction of rituximab has probably been the second major breakthrough in TTP management. Rituximab is now routinely recommended during the acute phase, typically in patients with a suboptimal response to treatment, or even as frontline therapy, with high response rates. In more severe patients, salvage strategies may include twice daily TPE, pulses of cyclophosphamide, vincristine, as well as splenectomy in the more desperate cases. In this life-threatening disease, relapses can be efficiently prevented in patients with a severe acquired ADAMTS13 deficiency and otherwise in remission with the use of rituximab. In the coming years, the TTP therapeutic landscape should be enriched by original strategies stemming from clinical experience and new agents that are currently being evaluated in large, ideally international, clinical trials. Promising agents under evaluation include *N*-acetylcysteine, bortezomib, recombinant ADAMTS13 and caplacizumab, an inhibitor of the glycoprotein-Ib/IX-von Willebrand factor axis.

Contents

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a particular form of thrombotic microangiopathy (TMA), characterized typically by microangiopathic hemolytic anemia, profound peripheral thrombocytopenia and severe deficiency in the von Willebrand

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factor-cleaving protease ADAMTS13 (acronym for A Disintegrin And Metalloproteinase with ThromboSpondin-1 motifs; 13rd member of the family). ADAMTS13 deficiency is usually severe (<10%) and results from autoantibodies against ADAMTS13 (autoimmune TTP) or from biallelic mutations of the encoding gene. In some cases, autoimmune TTP occurs in association with specific conditions that have to be identified for appropriate management: HIV infection, connective tissue disease, pregnancy, cancer or treatment with antiplatelet agents [1].

The standard treatment of autoimmune TTP consists mainly of daily therapeutic plasma exchange (TPE) that allows ADAMTS13 repletion and, to a lesser extent, removal of anti-ADAMTS13 antibodies and possibly pro-aggregatory substances. TPE transformed the historically fatal prognosis of TTP, leading to the current overall survival rates of 85% [2]. In the last several years, further significant changes have been introduced in the management of autoimmune TTP. The identification of the central role of anti-ADAMTS13 antibodies in the pathophysiology of TTP [3] which is now considered an autoimmune disease, has led to wider use of immunosuppressive treatments. In this context, the introduction of rituximab has probably been the second major breakthrough in TTP management. However, the current knowledge about the use of rituximab in TTP is based on few studies with a limited number of patients and moderate levels of evidence. Moreover, these studies raised many questions that remain unsolved. Should rituximab be used as frontline therapy, or only in patients with a suboptimal response to TPE? Which is the optimal schedule of rituximab administration? Should rituximab be systematically used as preemptive therapy? Which strategy should be used when rituximab fails to improve ADAMTS13 activity? Lastly, there is no consensus concerning the management of patients with refractory disease and emerging therapies might bring new strategies in the future years. These topics are addressed in this review.

2. Treatment

2.1. Frontline treatment

TTP requires a rapid diagnosis and urgent management as a medical emergency. The immediate outcome may not be predictable and maximal resuscitative measures should be proposed. An older age, a very high LDH level (reflecting mostly organ damage) and an increased cardiac troponin level on diagnosis were associated with death and treatment refractoriness [2].

2.1.1. Plasma therapy

TPE with replacement of plasma remains the cornerstone of the current management of TTP. TPE (1.5x plasma volume exchange for the first procedures, followed by 1.0 × patient plasma volume thereafter) should be started as soon as the diagnosis of TTP is established or even suspected. TPE is performed daily until organ involvement has resolved, the platelet count has stably recovered and hemolysis has ceased. A theoretical superiority of cryosupernatant plasma, which is depleted of high molecular weight VWF multimers, has been suggested. However, this was not corroborated in a randomized, though small trial that demonstrated equipotency with plasma [2,4].

2.1.2. Steroids

There is a rational for the use of steroids in the treatment of autoimmune TTP given its autoimmune nature. However, the level of proof concerning steroid efficacy in the treatment of TTP remains quite low. Before the current systematic use of TPE in TTP, the administration of high-dose steroids alone had some efficacy, at least in patients without significant organ involvement since 30/54 patients (55%) responded to steroids in 48–72 h. High-dose methylprednisolone (10 mg/kg/day for 3 days and then 2.5 mg/kg/day) may be more efficacious than standard-dose (1 mg/kg/day) as an adjunctive treatment to TPE in patients with newly diagnosed TTP. Taken together, these results indicate that steroids might have a place in the management of TTP in association with TPE, although the modality of administration remains debatable [2,4].

2.1.3. Rituximab

The humanized anti-CD20 monoclonal antibody rituximab was first introduced in patients with a suboptimal response to TTP conventional treatment (i.e., disease exacerbation or refractoriness), while TPE was usually continued daily. In four retrospective studies, 57 patients with TTP were treated with rituximab (in most instances, 375 mg/m^2 in four weekly doses) after suboptimal response to standard treatment (Table 1) [5–8]. Remission was achieved in 51/57 (89%) cases, typically in less than 4 weeks. Six patients did not respond to treatment and three died. In three prospective studies [9–11], involving 71 patients with a suboptimal response to standard treatment, rituximab 375 mg/m^2 administrated within 2–3 weeks resulted in remission in 98% of cases within the first month of diagnosis (Table 1). No relapse was observed during the first year of follow-up, but there were relapses beyond one year. In neither study was rituximab associated with significant side effects. Recently, a rituximab regimen based on B cell depletion provided evidence that similar results could be obtained with only two to three rituximab infusions [11].

Whether rituximab should be reserved for patients who experience a suboptimal response to standard treatment or used as frontline therapy in all patients with autoimmune TTP is still debated. In 2011, the UK group [12] reported that frontline treatment with rituximab resulted in a shorter hospitalization and fewer relapses that occurred later than in a historical group not treated with rituximab (Table 1). Fewer and later relapses were also seen in rituximab treated patients by the French TMA Reference Center Network [10] and the Oklahoma TTP registry [8], prompting the suggestion that all autoimmune TTP patients should be treated up-front with rituximab in conjunction with TPE [13].

2.1.4. Other immunomodulators

Vincristine was used mainly in refractory TTP, in the pre-rituximab era. In a literature review on 56 studies and 105 patients, stable remission was achieved in 73% of patients receiving vincristine as secondary or salvage therapy. Today however, rituximab is usually preferred in autoimmune TTP. *Cyclosporine A* has been reported as an effective treatment in refractory TTP and as frontline treatment in association with TPE [4,14]. The clinical response correlates with improvement in ADAMTS13 activity and suppression of anti-ADAMTS13 antibodies. However, a recent randomized study reported that steroids were associated with a better improvement in ADAMTS13 activity than with cyclosporine A as a result of a more significant decrease in anti-ADAMTS13 antibodies concentration in serum, questioning its therapeutic role [15].

2.2. Management of the more severe forms

Rituximab might not be effective for the treatment of unresponsive TTP during the first two weeks, with a reported delay in the onset of its effect that may reach 27 days. No consensus has been reached on the best approach to treat refractory, life-threatening TTP. If a patient does not respond to standard TPE and prednisone, our current use is to increase the intensity of the treatment sequentially depending on the clinical course by adding rituximab, followed by twice daily TPE (Fig. 1), pulses of cyclophosphamide, bortezomib and even splenectomy in the more severe