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State of the art

Management of thrombotic thrombocytopenic purpura

Prise en charge du purpura thrombotique thrombocytopénique

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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, typically within the first days of management. In this context, the introduction of rituximab has 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, and increasingly as frontline therapy, with high response rates in the following weeks. In more severe patients, salvage strategies typically include twice daily TPE, pulses of cyclophosphamide, as well as splenectomy in the more desperate cases. In this life-threatening and debilitating 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, international, clinical trials. Promising agents under evaluation include caplacizumab (an inhibitor of the glycoprotein-Ib/IX-Von-Willebrand factor axis), N-acetylcysteine, recombinant ADAMTS13, and anti-plasmocyte compounds.

Keywords: Thrombotic thrombocytopenic purpura; ADAMTS13; Plasma exchange; Rituximab; Immunotherapy

Résumé

Les échanges plasmatiques (EP) quotidiens ont transformé le pronostic historiquement fatal du purpura thrombotique thrombocytopénique purpura (PTT) acquis, lié à des anticorps anti-ADAMTS13 (TTP), et permettent des taux de survie actuels de > 80 %. Cependant, des rechutes s'observent dans 40 % des cas et des situations de maladies réfractaires s'observent encore, typiquement dans les premiers jours de la prise en charge. Dans ce contexte, l'utilisation du rituximab a été la deuxième avancée majeure dans la prise en charge de la maladie. Le rituximab est actuellement recommandé au cours de la phase aiguë chez les patients, en réponse suboptimale au traitement standard et de plus en plus, comme thérapie de première ligne, avec des taux de réponse élevés dans les semaines suivant son introduction. Dans des formes les plus sévères, les stratégies de sauvetage incluent typiquement des EP deux fois par jour, des bolus de cyclophosphamide, ainsi qu'une splénectomie dans les cas les plus désespérés. Dans cette maladie potentiellement fatale, les rechutes peuvent être prévenues efficacement par des injections préemptives de rituximab chez les patients conservant un déficit sévère acquis en ADAMTS13 et par ailleurs en rémission. Dans les années à venir, de nouveaux agents thérapeutiques devraient enrichir l'arsenal thérapeutique dans le PTT. Ceux-ci devront être idéalement évalués dans le cadre d'essais cliniques internationaux. Ces agents en cours d'évaluation incluent le caplacizumab (un inhibiteur de la voie glycoprotéine Ib/IX-facteur Willebrand), la N-acétylcystéine, une protéine ADAMTS13 recombinante et des agents ciblant les plasmocytes.

Mots clés : Purpura thrombotique thrombocytopénique ; ADAMTS13 ; Échanges plasmatiques ; Rituximab ; Immunothérapie

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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 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 half of 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% [2,3]. 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, given the rarity of TTP and the resulting difficulty to drive large prospective trials, the current knowledge about the use of rituximab in this disease 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? In addition, there is no consensus concerning the management of patients with refractory disease and emerging therapies might bring new strategies in the future years. Lastly, most current deaths related to TTP result from a late diagnosis and a delayed intensive treatment, raising the need to provide more rapidly this diagnosis and to identify more rapidly patients at high risk of early death. 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 [2,3].

2.1.1. Plasma therapy

TPE with replacement of plasma remains the cornerstone of the current management of TTP. TPE (1.5 × 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].

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 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 (30/54 patients (55%) responded to steroids in 48–72 hours). 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 [1,3].

2.1.3. Rituximab

The humanized anti-CD20 monoclonal antibody rituximab (Mabthera®, Roche) that was originally developed to treat CD20+ B cell malignancies, 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, with the aim of suppressing the production of anti-ADAMTS13 antibodies. Four rituximab infusions were performed weekly or within 2 weeks, after a TPE session. One study suggested that an alleviated schedule consisting in only 2 to 3 infusions provided comparable results (Table 1). Remission was achieved in most cases, typically in less than 4 weeks. Rituximab was associated with a rapid and substantial depletion of peripheral B cells, more frequent and faster recovery of ADAMTS13 activity and more effective depletion of anti-ADAMTS13 antibodies within a 1-year period. 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 effect. 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. Two prospective studies [4,5] reported that frontline treatment with rituximab resulted in a shorter hospitalization and fewer relapses that occurred later than in a historical group