Case Report

Successful treatment of thrombotic thrombocytopenic purpura using low-dose rituximab combined with plasmapheresis: three case reports and literature review

Saisai Ren1,2*, Yanling Tao3*, Haihui Liu1,2, Hao Zhang2

1Graduate School, Jining Medical University, Jining 272000, Shandong, China; 2Department of Hematology, Affiliated Hospital of Jining Medical University, Jining 272129, Shandong, China; 3Department of Pediatrics, Affiliated Hospital of Jining Medical University, Jining 272129, Shandong, China. *Equal contributors.

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Abstract: Thrombotic thrombocytopenic purpura (TTP) is a haematological disorder which affects the arterioles and capillaries of multiple organs. We reported three cases of TTP successfully treated with low-dosage rituximab combined with plasmapheresis. All three cases were diagnosed according to the diagnostic criteria of TTP. A weekly doses of 100 mg rituximab was applied for four weeks of presentation (on day 1, day 8, day 15 and day 22) as a salvage treatment for relapsing/refractory disease in two cases and as a first-line treatment in one case. Resolution of clinical symptoms and hematological abnormalities occurred as early as the second dose, and after the completion of treatment, all three patients achieved complete response. They were currently free from relapse and the duration of complete response was 5-27 months. During the treatment course, all three patients were given with plasmapheresis in different times. The recommended quantity of plasmapheresis was 40 ml/kg once a day, and the plasmapheresis was stopped when platelet rose to 150×10^9/L, lasting 2 days. This report indicates that, rituximab exhibits short and long-term favorable effects for the treatment of TTP, and its combination with plasmapheresis may positivity support early salvage therapy in both acute/refractory and relapsing cases.

Keywords: Thrombotic thrombocytopenic purpura, plasmapheresis, rituximab

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a haematological disorder characterized by fever, neurological abnormalities, microangiopathic hemolytic anemia, renal failure and thrombocytopenia [1]. TTP can affect the arterioles and capillaries of multiple organs [2]. In diagnosis, the symptoms of fever, microangiopathic hemolytic anemia and thrombocytopenia are necessary [3]. As there is clinical overlap with haemolytic uraemic syndrome, autoimmune disease and a spectrum of pregnancy-related problems, the diagnosis of TTP is difficult [4]. The current frontline treatment is still plasmapheresis and application of steroids [5, 6]. Therefore, it is vital important to make differential diagnosis with these diseases that evolve with microangiopathic hemolytic anemia in a short time to initiate the plasmapheresis [7]. Although plasmapheresis can effectively reduce the mortality to approximately 20% [8], there is a significant subset of patients with either delayed or absent responses, requiring protracted courses of plasmapheresis with a high rate for the associated complications [9].

Rituximab is a chimeric monoclonal antibody against the CD20 antigen expressed on B lymphocytes. The proposed mechanism of action of this drug in the treatment of this condition is its clearance of CD20-positive B cells. It has been used for relapsing or refractory TTP, which leads to high-rate and durable remission [8-11]. However, as a vital problem, the timing of initiation of rituximab administration currently remains to be determined [12], and the other challenge is that the long-term effects of rituximab-containing treatment of TTP have not fully been proven. Here, we reported three cases with TTP that were successfully treated with rituximab combined with plasmapheresis.
Rituximab combined with plasmapheresis for treating TTP

The diagnosis of the condition as well as evaluation of short- and long-term effects of the treatment was supported by sequential assessment. Finally, the related cases reported in the literatures were reviewed, and the indication and efficacy of early administration of rituximab for TTP were discussed.

Patients and methods

Patients

Three uninsured patients were diagnosed with TTP from March 2013 to January 2015 in Affiliated Hospital of Jining Medical University (Shandong, China). The diagnosis was established by the presence of many clinical findings of classic pentad. The microangiopathic hemolytic anemia was documented by the presence of two or more schistocytes on blood film, thrombocytopenia (platelet count < 100×10⁹/L), and elevated serum lactate dehydrogenase. This study was approved by the ethics committee of Affiliated Hospital of Jining Medical University. Written informed consent was obtained from all participants.

Treatment

Three patients received plasmapheresis with fresh-frozen plasma (2× plasma volume). Rituximab was administered at a weekly dose of 100 mg through intravenous for 4 weeks (on day 1, day 8, day 15 and day 22). Concerning on minimizing loss, rituximab was administered after a plasmapheresis procedure, and the latter was resumed at least 24 h after monoclonal antibody infusion. All patients received the equivalent of 1 mg/kg/day of prednisone for 1 week, and afterwards steroids were rapidly tapered [13, 14].

Evaluation of treatment outcome

Complete response (CR) was defined as the clearance of all clinical signs and symptoms, as well as the sustained normalization of biochemical and hematological parameters related to TTP. Relapse was considered when clinical and laboratory evidence of the disease was apparent after CR was obtained. Refractory disease was defined as the persistence of TTP despite treatment [15].

Results

The clinical and laboratory features of the patients at presentation and the treatment outcome were summarized in Table 1. The reports of these three cases were as follows.

Case 1

In March 2013, a 15-year-old boy presented with headache, fever, and mucocutaneous bleeding in both arms was admitted. Hematological, biochemical, and blood film morphology confirmed the diagnosis of TTP. Other diseases were not ruled out. The treatment with plasmapheresis and steroids was started, and the progressive improvement was obtained. The patient received a total of 11 times of plasmapheresis and 4 doses of rituximab, achieving CR with no relapse during the 27 months of follow-up.

Case 2

In June 2013, a 36-year-old male patient with mucocutaneous bleeding was admitted. The

Table 1. Clinical and laboratory features of the patients at presentation and the treatment outcome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)/gender</td>
<td>15/male</td>
<td>36/male</td>
<td>44/female</td>
</tr>
<tr>
<td>Underlying condition</td>
<td>No</td>
<td>TTP</td>
<td>No</td>
</tr>
<tr>
<td>Neurological manifestations</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>57</td>
<td>104</td>
<td>75</td>
</tr>
<tr>
<td>Platelets (×10⁹/L)</td>
<td>6</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>979</td>
<td>391</td>
<td>1353</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>Normal</td>
<td>50.8</td>
<td>Normal</td>
</tr>
<tr>
<td>Schistocytes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rituximab indication (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Days from first dose of rituximab to response</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Days to CR after rituximab</td>
<td>27</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Concomitant treatment</td>
<td>DXM</td>
<td>DXM</td>
<td>DXM</td>
</tr>
<tr>
<td>Number of plasmapheresis</td>
<td>11</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Duration of CR (month)</td>
<td>27</td>
<td>24</td>
<td>5</td>
</tr>
</tbody>
</table>

TTP, Thrombotic thrombocytopenic purpura; CR, Complete remission; DXM, Dexamethasone.
peripheral blood examination revealed the presence of abundant schistocytes. TTP was diagnosed and underlying 11-year TTP history was ruled out. It was considered as a relapse TTP. He was treated with plasmapheresis, steroids and rituximab (100 mg weekly) for 4 weeks as front-line treatment. During hospitalization he received 4 times of plasmapheresis and 4 doses of rituximab, achieving CR. The two additional doses of the antibody were administered during ambulatory follow-up. After more than 24 months he remained in CR.

Case 3

In January 2015, a 44-year-old woman presented with a nine-day discomfort of confusion and severe headache and a complaint of six-day mucocutaneous bleeding was admitted. A diagnosis of TTP was supported by laboratory findings and the plasmapheresis was initiated, followed by using low-dose rituximab. She completed 9 times of plasmapheresis, and immediately before the second dose of rituximab, a lowering in her hemoglobin and platelet count was documented, without clinical deterioration and no change in the number of schistocytes or other microangiopathic hemolytic anemia parameters. No additional therapy was initiated and her hemoglobin and platelet count gradually increased until reaching normal parameters. The fourth and last dose of rituximab was administered. During a 5-month follow-up she remained in CR.

Discussion

In this study, we present three cases of TTP including two cases with primary TTP and one case with seven-year history of TTP, concerning a relapse and refractory TTP. The three patients presented with a clearly suspicious clinical course, with the manifestation of severe microangiopathic anemia and thrombocytopenia on admission. Owing to laboratory restrictions we could not document the presence of an ADAMTS-13-directed antibody or low activity of the cleavage protein. In the case 2 and case 3, the clinical, hematological, and biochemical data were clear enough to justify the start of treatment, due to a severe and typical presentation. However, the case 1 took a relatively long time to make sure the diagnose.

TTP is a rare but life-threatening autoimmune disorder [16, 17]. What’s more, it is ever reported that, despite the use of the well-known and established treatment for TTP, the disease relapse occurs in 30-50% of cases [18]. This provides the necessity for seeking a better immunosuppressive regimen, ideally one with efficient short-term efficacy, lower relapse rate, and few side effects. To meet the standards, rituximab has been reported to be applied in refractory or relapsed cases of TTP with success [19-21]. Depletion of B-cells can prevent synthesis of this antibody and presumably induce remission of the disease [16, 17]. Rituximab was used as front-line treatment in all our cases, although in the second patient the disease was seven-year TTP. As mentioned above, rituximab has been applied successfully as salvage treatment for refractory and chronic relapsing case, which can reduce the times for plasmapheresis and potentially achieve the cure. Recently, Scully et al [22] demonstrated very favorable results using rituximab as front-line treatment for TTP, concluding that the group of patients receiving this treatment modality needed less plasmapheresis sessions and spent less time in the hospital, without serious complication.

The dose of rituximab had been used successfully in other autoimmune diseases. However, it had rarely been previously reported for the treatment of TTP. In previously published literatures [8, 11, 14, 23-27], rituximab has been initiated at a dose of 375 mg/m². In this study, considering that the evidence was available of rituximab success in TTP, the use of a low dose was justifiable, and it was an economically affordable regimen for this population of uninsured patients. We administered a rituximab dose of 100 mg weekly and last 4 weeks. The use of lower doses of rituximab has been shown to be effective in the treatment of other autoimmune diseases, such as acute hemolytic anemia, where B-cell depletion has been demonstrated to occur even at these low doses. Other potentially beneficial effects have also been shown in antigen presenting cell function, cytokine production and immune modulation including up-regulation of regulatory T cells [28-31]. The three patients in this presentation received low-dose rituximab with a markedly good outcome, and the number of plasmapheresis needed to achieve CR was similar with that used in patients receiving a dose of 375 mg/m² [8, 11, 14, 23-27]. It is particularly important to address the markedly good and sustained
response in cases 2 (a relapsed and refractory case), usually considered challenging case. Up to now, there is no evidence of relapse in any of the three cases during a follow-up of 27, 24 and 5 months, and it may support the low-dose rituximab benefit to our patients shown by the depletion of lymphocyte count during treatment. As suggested for other autoimmune cytopenias, low-dose rituximab should be considered as a viable option, including the possibility of achieving similar results to those obtained with the standard dose and the extra benefit of a reduction in treatment cost and potential complications.

In conclusion, it is markedly useful for our three TTP patients to initiate with low doses of rituximab, and the patients have achieved a complete and sustained response after treating with plasmapheresis and steroids as front-line treatment. In addition, low-dose rituximab can reduce the number of inpatient days and plasmapheresis sessions. The remarkable outcome in our report is markedly similar with that in cases previously described with the standard dose, which leads to considerable savings. Nevertheless, further study of a larger number of patients is needed to evaluate more precisely the role of rituximab as front-line treatment, and to find out what dose of rituximab in TTP is optimal.

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Disclosure of conflict of interest

None.

Address correspondence to: Hao Zhang, Department of Hematology, Affiliated Hospital of Jining Medical University, No. 89 Guhuai Road, Jining 272129, Shandong, China. E-mail: cnzhdoc@163.com

References

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