Wspolczesna Onkol 2013; 17 (2): 222–224

DOI: 10.5114/wo.2013.34629

Case report

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder, for which rituximab has been proven to be an effective treatment. The response rate was reported to be approximately 60% in refractory ITP patients. However, the response time is slower than expected, and the mechanism of action of rituximab in ITP is still unclear. Thus, sometimes, the use of a combination therapy with rituximab according to different patient conditions is necessary. We report two refractory chronic ITP cases. The two patients were administered a low dose of dexamethasone (10 mg, weekly) combined with rituximab and a smaller dose of prednisone (10 mg, daily) as maintenance therapy. Although their peripheral B cells were almost eliminated, no complete reaction was observed. The maintenance therapy with prednisone was helpful in the prevention of bleeding. The patients' responses to rituximab treatment suggest that multiple immunological mechanisms are involved in ITP pathogenesis and that the use of a combination therapy with rituximab according to the different patient conditions is necessary.

Key words: immune thrombocytopenic purpura, rituximab, dexamethasone, prednisone.

Combination therapy of rituximab and corticosteroids for patients with refractory chronic immune thrombocytopenic purpura: report of two cases

Yun Ling, Xinyu Qian, Xiangshan Cao

Department of Hematology, the First People's Hospital of Changzhou, Changzhou, Jiangsu, China

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder. Corticosteroids, usually prednisone, are often the first-line treatment for ITP. However, about 70% of adult patients experience a relapse after the discontinuation of corticosteroids. Moreover, approximately 20% to 30% of chronic ITP patients do not respond to corticosteroid therapy [1, 2]. Rituximab has been proven to be an effective treatment for ITP, and the response rate was reported to be about 60% in refractory ITP patients [3]. However, the response time with rituximab is slower than expected, and at least three months might be necessary to observe an effect. Therefore, sometimes, the use of a combination therapy with rituximab according to different patient conditions is necessary. For this reason, we performed a clinical analysis of the combination therapy of rituximab and corticosteroids in two patients to evaluate the efficacy and safety of this treatment.

Case report

Case 1

An 82-year-old man presented with sustained blood-tinged sputum and bleeding in the skin for more than six months. He has a history of hypertension, and his platelet count was about 1×10^9 to 10×10^9/l. No splenomegaly was observed. His bone marrow showed an increased number and maturity disturbance of megakaryocytes without morphological evidence of dysplasia, and his platelet-associated immunoglobulin G (PAIgG) level was normal. His antinuclear antibody and rheumatoid factor test results were negative. He was diagnosed with chronic ITP, based on the criteria reported in a previous paper [4]. He was initially treated with prednisone, 40 mg/day, which resulted in a rapid increase in his platelet count to around 100×10^9/l. However, he developed steroid-induced diabetes after a short-term prednisone therapy and relapsed on a prednisone taper, with his platelet count decreasing to 18×10^9/l. His blood glucose was controlled after insulin therapy. No response to the second course of 40 mg/day prednisone was observed. He refused splenectomy and other immune suppressive drugs, and thus we gave him weekly intravenous infusions of 375 mg/m^2 of rituximab for four weeks combined with 10 mg of dexamethasone. After his first dose of dexamethasone followed by rituximab, within 24 h, his platelet count had increased to 65×10^9/l and his bleeding symptoms were significantly improved. During the succeeding three-week treatment period, his platelet count fluctuated between 30×10^9/l and 60×10^9/l and then dropped to a minimum of 19×10^9/l. Considering the patient's slow response

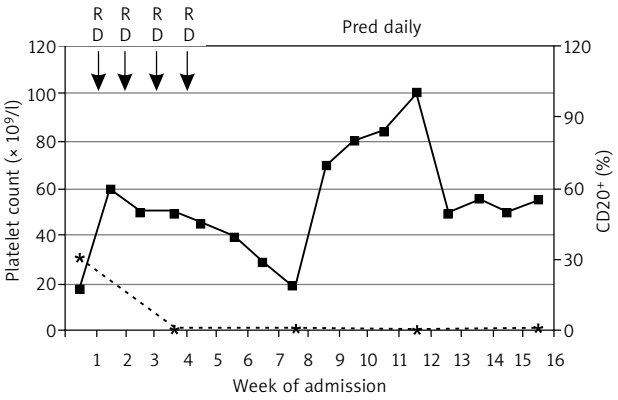

Fig. 1. Clinical course of patient 1. Timeline linear graph of platelet counts (solid line) and percentage of CD20 positive cells (dotted line), coinciding with rituximab (R) and dexamethasone (D) (arrows) and prednisone (bar) therapy

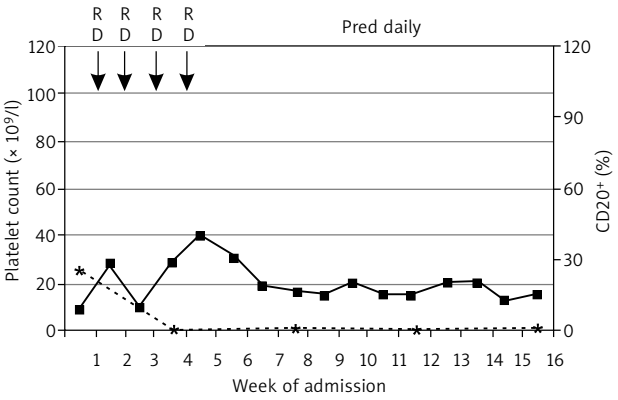

Fig. 2. Clinical course of patient 2. Timeline linear graph of platelet counts (solid line) and percentage of CD20 positive cells (dotted line), coinciding with rituximab (R) and dexamethasone (D) (arrows) and prednisone (bar) therapy

to rituximab and for the prevention of bleeding, we still gave the patient a maintenance therapy of 15 mg of prednisone daily, and consequently his bleeding stopped. Two months after his initial rituximab and dexamethasone treatment, the patient's platelet count began to recover gradually to normal and then the platelet count stabilized at above 70 × 10^9/l for one month. When his prednisone dosage was tapered from 15 mg/day to 10 mg/day, his platelet count dropped again to around 50 × 10^9/l. Interestingly, a very low CD20 expression level was continuously observed throughout the treatment period (Fig. 1).

Case 2

The second case concerns a 15-year-old female patient, who was diagnosed with ITP at the age of seven. Initially, she was treated with prednisone daily and had a favorable response. However, large prednisone doses of 40 mg/day were needed to maintain the efficacy, and several steroid tapers resulted in her repeated relapses of ITP. She then received dexamethasone and intravenous immunoglobulin therapy, after which her platelet count recovered to normal for a short period and then dropped again. Subsequently, danazol and 6-mercaptopurine were administered, but the thrombocytopenia persisted. The patient presented with ecchymosis, heavy menstrual bleeding, Cushing's syndrome, and a platelet count of 8 × 10^9/l. For her refractory chronic ITP, the patient received a weekly dose of 100 mg of rituximab combined with intravenous dexamethasone (10 mg) for four weeks. However, her platelet count remained less than 30 × 10^9/l after the treatment. We gave her a daily maintenance therapy of 10 mg of prednisone, and consequently her bleeding symptoms were significantly improved. Similar to the result of the previous case, her CD20 expression level was constantly low after treatment with rituximab (Fig. 2).

Discussion

Immune thrombocytopenic purpura is an autoimmune disorder characterized by antiplatelet autoantibody-mediated platelet destruction in the reticuloendothelial system. Platelet autoantibody production results from autoreactive T-helper cell activation and autoreactive T-B cells cognate interaction. The activation and expansion of autoreactive T cells are induced by antigen-presenting cells in the spleen that present apoptotic platelets to T cells [5–7]. The mechanism of action of rituximab (a monoclonal anti-CD20 antibody) in ITP may be due to the selective depletion of $CD20^+$ B cells, which affects autoantibody development and normalizes abnormal autoreactive T-cell responses in patients with ITP [8]. The peripheral B cells of the two patients were almost eliminated even at different doses of rituximab. Although the platelet count of the male patient was significantly improved, it was continuously below the normal level. For the female patient, no favorable response to rituximab was observed. The result suggests that ITP is a heterogeneous disorder. Not only B cells but also cytotoxic T lymphocytes [9] or other unknown factors that do not depend on B cells might play important roles in the pathogenesis of ITP. Considering the varying treatment effect of rituximab in different ITP patients, as well as the slow response time, we believe that the use of combination therapy with rituximab for refractory ITP patients. Moreover, because both patients had steroid-related complications such as steroid-induced diabetes and Cushing's syndrome, we used a low dose of dexamethasone (10 mg, weekly) combined with rituximab and a smaller dose of prednisone (10 mg, daily) as maintenance therapy. In the first case, the quick increase in platelet count after the first administration of rituximab and dexamethasone might be an effect of the steroid, which resulted in a rapid improvement of the patient's bleeding symptoms. The maintenance therapy with low-dose prednisone was helpful in the prevention of bleeding even with very low platelet counts (below 30 × 10^9/l). The patients' responses to rituximab treatment suggest that multiple immunological mechanisms are involved in ITP pathogenesis and that the mechanism of action of rituximab in ITP needs to be further investigated.

The authors declare no conflict of interest.

References

1. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. Am J Hematol 2010; 85: 174-80.
2. Bromberg ME. Immune thrombocytopenic purpura – the changing therapeutic landscape. N Engl J Med 2006; 355: 1643-5.
3. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med 2007; 146: 25-33.
4. Semple JW, Milev Y, Cosgrave D, Mody M, Hornstein A, Blanchette V, Freedman J. Differences in serum cytokine levels in acute and chronic autoimmune thrombocytopenic purpura: relationship to platelet phenotype and antiplatelet T-cell reactivity. Blood 1996; 87: 4245-54.
5. Kuwana M, Kaburaki J, Kitasato H, Kato M, Kawai S, Kawakami Y, Ikeda Y. Immunodominant epitopes on glycoprotein IIb-IIIa recognized by autoreactive T cells in patients with immune thrombocytopenic purpura. Blood 2001; 98: 130-9.
6. Kuwana M, Okazaki Y, Kaburaki J, Kawakami Y, Ikeda Y. Spleen is a primary site for activation of platelet-reactive T and B cells in patients with immune thrombocytopenic purpura. J Immunol 2002; 168: 3675-82.
7. Catani L, Fagioli ME, Tazzari PL, et al. Dendritic cells of immune thrombocytopenic purpura (ITP) show increased capacity to present apoptotic platelets to T lymphocytes. Exp Hematol 2006; 34: 879-87.
8. Stasi R, Del Poeta G, Stipa E, Evangelista ML, Trawinska MM, Cooper N, Amadori S. Response to B-cell-depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. Blood 2007; 110: 2924-30.
9. Olsson B, Andersson PO, Jernås M, Jacobsson S, Carlsson B, Carlsson LM, Wadenvik H. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. Nat Med 2003; 9: 1123-4.

Address for correspondence

Prof. **Xiangshan Cao**
Department of Hematology
the First People's Hospital of Changzhou
No. 185 Juqian Road, Changzhou 213000, Jiangsu, China
tel. +86-519-68871093
e-mail: xshcao@126.com

Submitted: 24.07.2011
Accepted: 25.01.2012