Maintenance Therapy with Rituximab in Adult Patients with Immune Thrombocytopenia

Marica Pavkovic, Slobodanka Trpkovska-Terzieva, Tatjana Sotirova, Lidija Cevreska, Aleksandar Stojanovic

University Clinic for Hematology, Medical Faculty, Ss Cyril and Methodius University Skopje, Republic of Macedonia

Abstract

Immune thrombocytopenia (ITP) is an autoimmune disease of unknown etiology, characterized by isolated thrombocytopenia and the absence of any underlying cause for thrombocytopenia. Corticosteroids are the standard first line treatment for patients with symptomatic disease, inducing platelet count recovery in 70-80% of patients; but in many cases, steroid tapering or withdrawal is followed by a decrease of platelet count and the need for additional treatment. Splenectomy is still the standard salvage therapy in cases refractory to corticosteroid therapy. In the past decade monoclonal anti-CD20 antibodies (Rituximab) are being increasingly used in patients with refractory ITP and other autoimmune diseases. Recent studies show that Rituximab is useful in the treatment of patients with chronic and refractory ITP. We report two cases with chronic ITP treated with standard dose of Rituximab in four weekly doses and than continue to receive maintenance therapy with Rituximab for 2 years.

Introduction

Immune thrombocytopenia or immune thrombocytopenic purpura (ITP) is an autoimmune disease of unknown etiology, characterized by thrombocytopenia due to the presence of platelet autoantibodies specific for platelet membrane glycoproteins, such as GPIIb/IIIa, GPIb/IX and GPIa/IIa [1]. These autoantibodies cause an increased destruction of autoantibody-opsonized platelets by FcγReceptor bearing phagocytic cells and impaired megakaryocyte maturation with reduced platelet production [2]. The etiology of ITP remains unclear, but both genetic and environmental factors are thought to play role in the development of the disease. ITP in adults is a chronic condition with insidious onset and varying severities of thrombocytopenia, more common in women than in men (2:1).
According to the recent international consensus report [3], ITP is characterized by isolated thrombocytopenia, defined as platelet count <100x10^9/L and the absence of any underlying cause for thrombocytopenia. It can be classified by duration into newly diagnosed, persistent (3-12 month duration) and chronic (>1 year duration). Because severe bleedings are rare in patients with ITP and they occur when platelet counts are <10x10^9/L, the main goal of therapy is to maintain a safe platelet count (not necessarily a normal count) to prevent major bleeding and to avoid adverse effects of therapy [4].

Glucocorticosteroids are the standard first line treatment for patients with symptomatic disease, inducing platelet count recovery in 70-80% of patients; but in many cases, steroid tapering or withdrawal is followed by a decrease of platelet count and the need for additional treatment [5]. Splenectomy is still the standard salvage therapy in cases refractory to corticosteroid therapy. About 40% of splenectomized patients either do not respond or relapse after surgery [6], approximately 10% of patients have early perioperative or delayed infections, and some develop surgical complications, although rarely fatal. In case of relapse or resistant to corticosteroids ITP, other immunosuppressive drugs can be used including azathioprine, cyclosporine A, cyclophosphamide, danazol, mycophenolate mofetil, all with marginal efficacy [7-11]. Intravenous immunoglobulin (IVIG) and anti-D are also used in the treatment of ITP, especially when rapid improvement of platelet count is needed (in case of life-threatening bleeding or prior to splenectomy or other surgical procedures). However, neither modality induces a long-term remission [12]. Recently, romiplostim and eltrombopag, two new thrombopoetin receptor agonists, have shown potent activity in ITP, but these agents do not act on the underlying disease mechanism, and therapeutic efficacy is dependent on continual administration [13, 14].

Rituximab is a chimeric monoclonal antibody specific for CD20 antigen that is expressed on mature B cells. Rituximab administration cause marked, but transient B-cell depletion, and this effect has been used for the treatment of several autoimmune diseases [15-17]. Rituximab is most commonly used in dose of 375mg/m^2, in four consecutive weekly doses, and it induce overall early response rate in patients with chronic ITP of 40-70% with complete response rate of 20 to 50% [18,19]. Bhagirath et al. [20] have used Rituximab in chronic relapsing thrombotic thrombocytopenic purpura (TTP) in 4 doses (375 mg/m^2) every four months for one year, after initial induction treatment. This agent is consider as safe, although few recent studies reported toxicities, including death (not necessarily attributable to rituximab) in nearly 3% of cases [18]. Long term therapy with Rituximab is associated with increased risk of infections like hepatitis B reactivation, herpes zoster reactivation, progressive multifocal leukoencephalopathy, etc. More prospective randomized trials are necessary to evaluate long-term efficacy and safety of Rituximab in the treatment of patients with ITP.

In this paper we report two female patients with chronic steroid-dependent and refractory ITP treated with Rituximab in our institutions. Patients with steroid-dependent and refractory ITP represent significant medical problem due to a constant need of treatment and frequent medical controls. Management of these patients refractory to standard treatment with corticosteroids and splenectomy is difficult, because the response rates to all available treatments at the moment is low and are not long-lasting [4].

Case report

Two female patients with chronic refractory or unresponsive ITP were treated with maintenance therapy with Rituximab in our institution. Both patients met the diagnostic criteria for ITP a) platelet count below 100x10^9/L in peripheral blood, b) normal or increased megakaryoposes on bone marrow examination, and c) the absence of clinically apparent associated conditions or causes of thrombocytopenia like lymphoproliferative disease, chronic liver disease, HIV infection, or other viral or bacterial infections. The medical records of these patients were reviewed for the clinical and laboratory information regarding their diagnosis, initial treatment, splenectomy and after treatment follow-up. The severity of thrombocytopenia was classified into: severe (platelets<30x10^9/L); moderate (platelet count:30-50x10^9/L) and mild (platelets >50x10^9/L).

Rituximab was administered at a dose of 375mg/m^2 intravenously once weekly for a total of 4 infusions (days 1, 8, 15 and 22) on an outpatient basis. Maintenance therapy was continued every three months for two years at a dose of 375mg/m^2. Response was evaluated after 4 weeks of treatment. The response criteria to Rituximab treatment were defined as: complete response (CR), a rise of platelet counts >100x10^9/L; partial response (PR), a rise of platelet counts >30x10^9/L; and no response (NR) when there was no rise in platelet count >30x10^9/L.
Case Report

Case 1

First case is a female patient born 1974, diagnosed with ITP in 1997 at the age of 23 years. She referred to our Clinic due to isolated thrombocytopenia and skin hemorrhage, without any other symptoms and physical findings. Platelet count at diagnosis was $14 \times 10^9/L$, with normal hemoglobin level and leukocyte count, and normal peripheral blood smear. Bone marrow analysis showed increased number of megakaryocytes, with otherwise normal hematopoiesis. Abdominal ultrasound was normal, as well as all biochemical and serological analysis. Diagnosis of primary immune thrombocytopenia or ITP was made and we started with first-line treatment with prednisone in standard dose of $1 \text{mg/kg}$. After 1 month platelet count have rose to $83 \times 10^9/L$, but started to decrease to $20 \times 10^9/L$ with steroid tapering. After 10 months from diagnosis she was splenectomized, due to severe thrombocytopenia resistant to corticosteroid treatment (Figure 1). Three years after splenectomy platelet count was normal and above $150 \times 10^9/L$, then it started to decrease bellow $100 \times 10^9/L$. Relapse was noticed in March 2001 with drop of platelet count to $7 \times 10^9/L$. Abdominal CT scan was normal (no signs of accessory spleen) and we started with Rituximab treatment at a dose of $375 \text{mg/m}^2$ in four weekly doses. One month after the 4th dose of Rituximab platelet count rose to maximum of $97 \times 10^9/L$ and partial response was achieved. We continued with maintenance therapy with Rituximab at the same dose, every three months for two years (total of 8 doses). During those two years platelet count was between 50 and $100 \times 10^9/L$. At the end of this period drop in a platelet count to $3 \times 10^9/L$ was registered and we started with prednisone at low doses of $25 \text{mg/day}$. During those two years platelet count was between 50 and $100 \times 10^9/L$. At the end of this period drop in a platelet count to $3 \times 10^9/L$ was registered and we started with prednisone at low doses of $25 \text{mg/day}$. Two months after prednisone was initiated, platelet count has risen to $93 \times 10^9/L$. Corticosteroid treatment last for 18 months and it was stopped due to stable platelet count between 50-100x10^9/L and no hemorrhagic symptoms. Since the beginning of year 2006 patient is without therapy, with platelet count between 50-100x10^9/L and no symptoms. Last control was in December 2010 when platelet count was $137 \times 10^9/L$ without any treatment (Figure 1). In this case, Rituximab induced partial response that last during the treatment and relapse of ITP was diagnosed just when maintenance therapy was finished. The benefit of treatment with Rituximab was no need of corticosteroid treatment for more than 2 years.

Case 2

Second case is also a female patient born 1969, diagnosed with ITP in 1980 at the age of 11 years and she was treated at Pediatric Department with corticosteroids for 6 months with good initial response. She had two successful pregnancies in 1988 and 1992 without any treatment for ITP. She referred to our Clinic for the first time in 1996, due to isolated mild thrombocytopenia, without any symptoms and physical findings (Figure 1). Platelet count at diagnosis was $56 \times 10^9/L$, with normal hemoglobin level and leukocyte count, and normal peripheral blood smear. After 6 months of follow up without treatment, platelet count dropped to $6 \times 10^9/L$ and she complained to prolonged menstrual bleeding. Bone marrow analysis was done and showed increased number of megakaryocytes, with otherwise normal hematopoiesis. Abdominal ultrasound was normal, as well as all biochemical and serological analysis. We started with first-line treatment with prednisone at standard dose of $1 \text{mg/kg}$. Response to corticosteroids was slow and partial, with raise in platelet count to maximum of $77 \times 10^9/L$. Every time when we try to decrease or stop prednisone, platelet count started to drop to values bellow $20 \times 10^9/L$. Patient was dependent to corticosteroid treatment with platelet count constantly below $20 \times 10^9/L$ and hemorrhagic symptoms like genital bleeding, epistaxis, and skin purpura. She also had complication in a form of herpes virus infection due to immunosuppressive therapy with corticosteroids. She refused to proceed with splenectomy. We have performed second examination of bone marrow with the same findings of increased megakaryopoiesis. In January 2003, we started Rituximab treatment at dose of $375 \text{mg/m}^2$ in four weekly doses (Figure 2). One month after the last dose of Rituximab platelet count rose to maximum of $94 \times 10^9/L$ and partial response was achieved. We continued with maintenance therapy with Rituximab at the same dose, every three months for two years (total of 8 doses). During those two years platelet count was between 50 and $150 \times 10^9/L$. She had partial response to Rituximab and one year after the last dose of Rituximab she was without any therapy, with platelet count between 50 and $100 \times 10^9/L$. In September 2005, drop in platelet count to $3 \times 10^9/L$ was noticed and prednisone treatment was started again. Partial response was achieved. In the

Figure 1: Response to different treatments in Patient No.1.
period of 2006-2010 she was dependent on corticosteroids with platelet count between 50-100 x 10^9/L. Every time when we stopped prednisone, marked drop in platelet count to 2-3 x 10^9/L was noticed. Last control was in December 2010 when platelet count was 22 x 10^9/L with low dose of prednisone (10 mg per day). In this case also, Rituximab induced only partial response that last during the treatment and relapse of thrombocytopenia was diagnosed 1 year after maintenance therapy was finished. The benefit of treatment with Rituximab was no need of corticosteroid treatment for more than 3 years.

Discussion

Management of patients with ITP refractory to standard treatment with corticosteroids and splenectomy is difficult, because the response rates to all available treatments at the moment are low and are not long-lasting. In the past decade monoclonal anti-CD20 antibodies (Rituximab) are being increasingly used in patients with refractory ITP and other autoimmune diseases. There are many studies reporting the results of Rituximab therapy in patients with ITP. Arnold et al. [18] systematically reviewed literature and referred overall response rate of 62.5% with significant toxicities, including dead in 2.9% of cases. Stasi et al. [21] showed that 10 of 25 patients with chronic and refractory ITP, already treated with 2 to 5 lines of treatment, respond to Rituximab and this response was maintained for 6 months or longer in 28% of patients. Results from this study indicate that rituximab therapy has a limited but valuable effect in patients with chronic ITP. Due to its mild toxicity and the lack of effective alternative treatments for patients with refractory ITP, Rituximab should be considered in patients who do not respond to first and second line of treatment.

Garcia-Chavez et al. [22] reported a 67% sustained response in 18 pretreated ITP patients, while Godeau et al. [23] reported promising 1-year response in 40% of patients. Aleem et al. [24] retrospectively studied 24 patients with refractory ITP, treated with Rituximab and 34% of patient’s sustained response after 6 months, 24% responses sustained after 1 year. Zaja et al. [25] conducted the first randomized clinical trial in which they have compared the efficacy of treatment with Rituximab+Dexamethasone and Dexamethasone alone, in 103 newly diagnosed or chronic patients with ITP that have not received any treatment before (treatment-naïve patients).

Arnold et al. [26] performed a pilot randomized trial to determine the feasibility of recruitment, protocol adherence, and blinding of a larger trial of rituximab versus placebo; and to evaluate the potential efficacy of adjuvant rituximab in ITP. Nonsplenectomized adults with newly diagnosed or relapsed ITP who were receiving standard ITP therapy for a platelet count below 30 x 10^9/L were randomly allocated to receive 4 weekly infusions of 375 mg/m^2 rituximab or saline placebo. Sixty patients were recruited over 46 months, which was slower than anticipated. After 6 months, there was no difference between rituximab and placebo groups for the composite outcome of any platelet count below 50 x 10^9/L, significant bleeding or rescue treatment once standard treatment was stopped.

Results from this study indicate that the combination of Dexamethason and Rituximab improves patient outcomes without compromising the safety. The relatively sustained duration of response in some patients suggests a beneficial effect and this treatment gives an option for second-line therapy, particularly in patients not responding to steroids and as an alternative to splenectomy.

Long term therapy with Rituximab may have potentially harmful effects, including the risk of hepatitis B reactivation, herpes zoster reactivation, progressive multifocal leukoencephalopathy, etc. These long-term side effects are well known and described in lymphoma patients treated with rituximab [27,28] but fortunately there were rare in patients with ITP treated with monoclonal anti-CD20 antibodies [18]. Most common adverse events of Rituximab treatment in ITP patients were infusional reactions and infections like pneumonia and meningitis [18].

Our results from two patients with refractory ITP were similar to already repotted results from other studies. Previous studies didn’t use maintenance therapy, only four weekly doses of Rituximab. We used maintenance therapy with Rituximab and we report our experience with it. Both patients had partial response to Rituximab treatment and response sustained for short period (1
year in second case, and only during the maintenance therapy in the first case). We didn’t observe any side effects from Rituximab treatment and the benefit from it was no need of other therapy and unwanted side effects from it (ex. steroids, cyclophosphamide, or other immunosuppressive agents).

In conclusion, Rituximab is well tolerated agent and could be useful in the treatment of some patients with refractory or unresponsive ITP, despite the relatively low response rate and short sustained remissions.

References


