Chronic Refractory Idiopathic Thrombocytopenic Purpura (ITP) and Anti-CD20 Monoclonal Antibody: A Case Report

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Summary: Idiopathic thrombocytopenic purpura (ITP) is an immune-mediated disorder characterized by accelerated and premature destruction of platelets by reticuloendothelial system. CD20, a transmembrane B-cell-specific antigen, is a potential target for treatment of certain malignant and nonmalignant plasma cell disorders including refractory ITP. Rituximab is a genetically engineered human anti-CD20 monoclonal antibody, which is approved for the treatment of low-grade non-Hodgkin's lymphoma. Recent clinical reports suggest that rituximab may be useful in treating certain patients with chronic refractory ITP. A 59-year-old woman with refractory ITP was placed on rituximab (four weekly doses of 375 mg/m^2) and her condition and platelet count were observed for 18 months. There was a gradual increase in platelet count and she was symptom free in this period and no side effects of the drug were reported. Anti-CD20 antibodies are likely to be used in the treatment of refractory ITP cases, but further studies about treatment schedule and criteria for patient selection should be done.

Key Words: Idiopathic thrombocytopenic purpura—Anti CD20 antibody—Rituximab.

CASE PRESENTATION

A 59-year-old woman was admitted to the hospital because of spontaneous subcutaneous hemorrhage and petechial rashes. The patient had been well until 1 week before she noticed some skin lesions and spontaneous mucosal bleeding. She did not take any medication and in her past medical history she had undergone hysterectomy because of a documented nonmalignant endometrial proliferation 15 years earlier. On admission, her temperature was 37.2°C and blood pressure 120/80 mmHg. Physical examination showed no splenomegaly and no other abnormalities except petechial rashes on extremities. Peripheral blood smear showed severe thrombocytopenia.

Complete blood count revealed hemoglobin (Hb) 13.2 g/dL, white blood cell (WBC) 4000/m^3 with normal differentiation and platelet (Plt) 8000/dL (Table 1). Serum protein electrophoresis was normal. Direct and indirect Coombs' test was negative. Serologic markers for infectious disease (including toxoplasmosis, human immunodeficiency virus [HIV], hepatitis A, B, and C viruses [HAV, HBV, and HCV], and Epstein-Barr virus [EBV]) were negative. C3, C4, and CH50 were normal (29%, 125%, and 94%, respectively) and antinuclear antibody (ANA) were negative. Cutaneous tuberculin test was 5 mm. Her chest x-ray and abdominal ultrasonography revealed no pathologic findings. A bone marrow biopsy showed normal cellular maturation and increased megakaryocytes.

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Clinical and Applied Thrombosis/Hemostasis
Vol. 12, No. 4, October 2006 489-492
DOI: 10.1177/1076029606293439

TABLE 1. Hematological Laboratory Results

Indices (Unit)	On Admission	After 2 weeks	After 2½ Years
Hct (%)	38.9	41.8	45.3
Hg (g/dL)	13.2	14.8	15
RBC (m^3)	4.59×10^6	5.17×10^6	5.14×10^6
MCV (fL)	85	83	88
MCH (pg)	29	31	29
MCHC (g/dL)	34	36	33
WBC (m^3)	4×10^3	13.1×10^3	6.1×10^3
Platelet (m^3)	8×10^3	360×10^3	280×10^3

Hct = hematocrit; Hg = hemoglobin; RBC = red blood cell; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; WBC = white blood cell.

A diagnosis of idiopathic thrombocytopenic purpura (ITP) was made. She was placed on oral prednisolone 75 mg/day and her Plt count increased to $360 \times 10^3/m^3$ by the end of second week. In the fourth week when she received 50 mg/day of prednisolone, Plt count dropped to $80 \times 10^3/m^3$.

Over the next 2 months, because she had some adverse effects of the corticosteroid (dyspepsia and generalized edema), prednisolone was tapered to 7.5 mg every other day and danazol 400 mg/day was begun. The Plt count was between 40×10^3 and $80 \times 10^3/m^3$ and she was symptom-free.

In the sixth month, again she experienced spontaneous mucosal bleeding and the Plt count dropped to $8 \times 10^3/m^3$. She was admitted to the hospital and received hydrocortisone 400 mg/day and high-dose intravenous immunoglobulin (IVIG) 400 mg/kg for 5 days, which gave a transient increase in Plt count that dropped again after 2 weeks.

She underwent splenectomy and its pathology revealed reactive hyperplastic change. On the second day after surgery her Plt count was $86 \times 10^3/m^3$ but dropped to less than $10 \times 10^3/m^3$ on the fourth day. She was placed on high-dose methylprednisolone 1500 mg/day that gave no response. After 2 weeks her Plt count was less than $10 \times 10^3/m^3$ and she had a bloody secretion in her drain bag. She received two courses of vincristin 1 mg/week with no increase in Plt count.

A bone marrow biopsy was repeated and specimens reviewed by an expert hematologist were compatible with ITP and there was no myelodysplastic or neoplastic change.

After about 9 months of treatment the patient was refractory to medications, Plt count was less than $50 \times 10^3/m^3$, and her mucosa surfaces had easy bruising (Fig. 1). Finally we decided to place the patient on anti-CD20 monoclonal antibody, rituximab. She received the drug in four weekly doses of 375 mg/m^2 and her Plt count increased to $188 \times 10^3/m^3$) in 2 months. About 18 months after treatment the patient has no complaint, does not have a Plt count of less than $80 \times 10^3/m^3$, and her Plt count has increased gradually.

DISCUSSION

ITP is an immune-mediated disorder characterized by accelerated and premature destruction of platelets by the reticuloendothelial system (1). Spontaneous remission is rare in adult patients but about 50% of cases respond to primary treatments including corticosteroid, IVIG, anti-RhD immunoglobulin, and splenectomy (2).

Chronic and refractory patients who fail primary modalities and experience sustained thrombocytopenia are difficult to manage. Treatments that aim at suppressing the production of autoantibodies and inhibiting macrophage-mediated destruction of opsonized platelets include danazol, cytotoxic/immunosuppressive chemotherapy agents (cyclophosphamide, vincristine, azathioprine), and the new anti-CD20 monoclonal antibody (2,3).

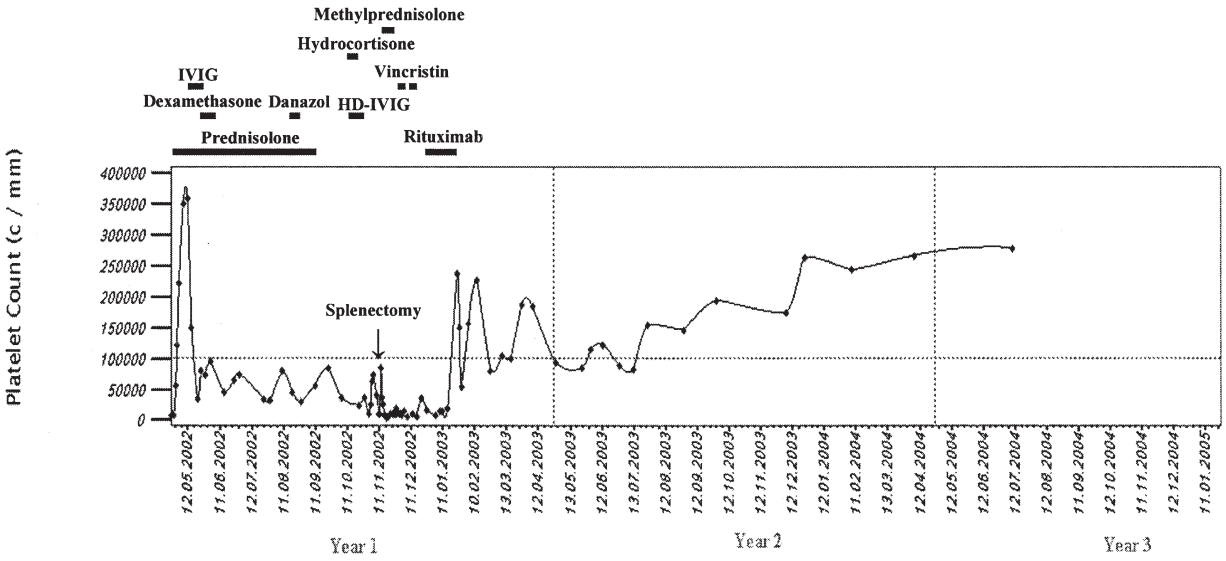

FIG. 1. Platelet count variation and treatment interventions.

CD20, a transmembrane B-cell-specific antigen, is a potential target for treatment of certain malignant and nonmalignant plasma cell disorders (4). Rituximab is a genetically engineered human anti-CD20 monoclonal antibody that is approved for the treatment of low-grade non-Hodgkin's lymphoma. Recent clinical reports suggest that rituximab may be useful in treating certain patients with chronic refractory ITP (3–10).

Possible mechanisms for rituximab's activity are the destruction of autoantibody-producing plasma cells and the blockade of immune effector cell-mediated destruction of antibody-coated platelets (4).

Perotta et al (10) have reported a series of 10 patients with chronic ITP who failed to respond initial treatments and 9 of whom had undergone splenectomy. Patients received rituximab 375 mg/m^2 weekly for 4 weeks. Five patients (50%) had a complete response (CR) (Plt count $> 100 \times 10^3/m^3$) and one (10%) had a partial response (PR) (Plt count 50–100 $\times$ $10^3/m^3$) and the duration of response was between 1 and 14 months.

Saleh et al (3) conducted a phase I/II clinical trial of 13 patients with refractory ITP. Rituximab was well tolerated with no obvious toxicity. PR was detected in two patients and lasted for 3 to 6 months and only one patient showed a CR for more than 6 months and all received full doses. Stasi et al (6) reported a cohort of 25 chronic ITP patients. In their study they found 5 patients with CR, 5 patients with PR, and 3 patients with a minor response (MR) (Plt count $< 50 \times 10^3/m^3$, with no need for continuous treatment) and overall response was 52%, which lasted for at least 6 months. There are also some anecdotal case reports of chronic ITP patients treated with rituximab that show promising results.

In the current reported case, as shown in Fig. 1, the patient was refractory to all medications after about 1 year of treatment, but when she received rituximab she experienced a CR for more than 18 months, with minimal side effects of the treatment. In the follow-up period, in the seventh month, her Plt count declined to less than $100 \times 10^3/m^3$, and there has been no need for any additional course of treatment.

In conclusion, we have no clear guidelines for management of chronic refractory ITP. Rituximab, as an anti-CD20 monoclonal antibody, shows some application in this field, but proper use of this treatment, alone and in combination with other modalities, needs further study.

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