Anti-CD20 monoclonal antibody therapy in refractory immune thrombocytopenic purpura

Multiple agents have been tried in patients with refractory immune thrombocytopenic purpura (ITP); however, none of these stands as a clear first choice. We administered rituximab, 375 mg/m^2 weekly × 4, to four patients with refractory ITP. With a median follow-up of 7 months, one patient has achieved a complete response, proving the possible efficacy of such a therapeutic modality in this context.

Patients with severe immune thrombocytopenic purpura (ITP) who do not respond to therapy within a 2-year period have a 4-fold increased mortality compared with the general population and a 4-fold increased morbidity compared with other patients.[1,2] This is why a variety of agents, including immunoglobulins, vinca alkaloids, danazol, colchicine, cyclophosphamide, and azathioprine have been used in these refractory patients.[3] Several authors have recently reported impressive results with anti-CD20 monoclonal antibody (rituximab) therapy in refractory ITP, with a complete response rate of 20% and an overall response rate of 52%.[4,5] Here we report on four patients who were treated for refractory ITP with rituximab, demonstrating the possible usefulness of such therapy in this clinical setting. Four outpatients who were in our care for treatment of refractory ITP were enrolled in the study after written informed consent was obtained. All 4 had had a relapse after at least 3 different therapies, and all patients were female. The patients' characteristics are listed in Table 1. Diagnostic criteria for ITP included the presence of isolated thrombocytopenia when all other causes of thrombocytopenia (lymphoproliferative disorders; myelodysplasia; agammaglobulinemia; congenital or hereditary thrombocytopenia; acquired human immunodeficiency virus, hepatitis B virus or hepatitis C virus infections; autoimmune disorders or drug related diseases) had been systematically excluded. A bone marrow aspirate with either normal or increased megakaryocyte count was available for all patients. All patients had achieved transient responses to intravenous immunoglobulin, a fact that supports the autoimmune nature of their condition.

Pretreatment platelet-associated IgG were identified using an immunocapture assay (Capture P, Immucor, Norcross, GA, USA). This test has been reported to have high sensitivity and specificity in ITP.[6] However, it is our experience and the experience of others[7] that this assay has a low likelihood ratio and weak positive and negative predictive values, probably because it detects IgG in platelet granules rather than true platelet autoantibodies.[8] Criteria for response were defined as follows: 1) complete response, a rise of platelets to more than 100×10^9/L; 2) partial response, a rise of platelets to counts between 50 and 100 ×10^9/L; 3) no response or refractory disease, when there was no rise in platelet count or a rise that did not exceed 50×10^9/L, with a need for continued treatment.

According to Saleh *et al.*[5] all patients received rituximab (Mabthera, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) 375 mg/m^2 weekly × 4, except 1 patient from whom therapy was withdrawn after the third dose due to severe symptomatic thrombocytopenia. Although all patients received intravenous premedication with hydrocortisone (100 mg) and diphenhydramine (5 mg), 1 patient had mild infusion-related side effects. One patient achieved a complete response, and the other 3 patients had no response. With a median follow-up of 7 months, no other delayed responses have ocurred. The cumulative platelet response in the 4 patients is depicted in Figure 1. It may be argued that the use of steroids in the premedication regimen could mask the response to rituximab, but the long follow-up in the only responder does not support this theory.

In conclusion, rituximab at 375 mg/m^2 weekly × 4 is well tolerated in refractory ITP and results in objective clinical responses, even in platelet associated-IgG negative patients as assessed by the Capture P assay. However, factors predictive of clinical outcome remain to be elucidated.

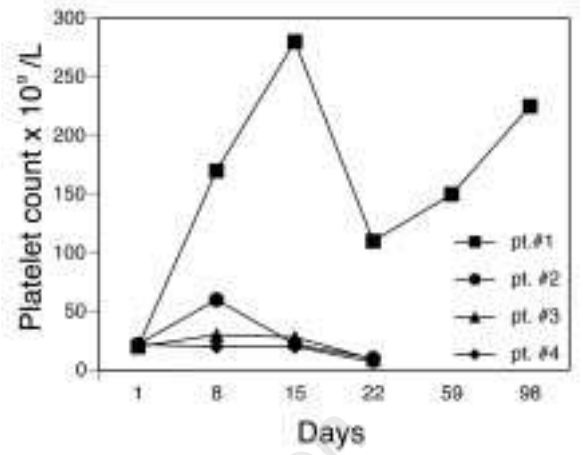

Figure 1. The cumulative platelet response in the 4 patients. Rituximab was infused on days 1, 8, 15 and 22, except to patient #2 from whom therapy was withdrawn after the third dose.

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Key words: rituximab, immune thrombocytopenic purpura, refractory.

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Table 1. Summary of patients' characteristics.

Case no.	Sex/Age (yr)	Duration of disease (yr)	Previous treatment	Splenectomy	PAIgG	No. of rituximab doses	Follow-up (mos)
1	F/55	8	Steroids, IVIg, danazol, azathioprine	Yes	Neg	4	7
2	F/37	1	Steroids, IVIg, azathioprine	No	Neg	3	7
3	F/54	5	Steroids, IVIg,	Yes	Neg	4	7
4	F/34	4	Steroids, IVIg, vincristine, cyclophosphamide, azathioprine, danazol	Yes	Neg	4	10

IVIg indicates intravenous immunoglobulin; PAIgG, platelet-associated IgG.

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Guido Finazzi, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Finazzi and the Editors. Manuscript received October 19, 2001; accepted January 3, 2002.