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Successful Treatment of Severe Refractory Idiopathic Thrombocytopenic Purpura With Liposomal Doxorubicin

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Idiopathic thrombocytopenic purpura (ITP) is refractory to initial treatment (steroids and splenectomy) in 25 to 30% of patients. These patients have a significant risk of fatal hemorrhage. Two patients with ITP refractory to multiple interventions and severe depression of platelet counts responded to treatment with liposomal doxorubicin with a return of platelet counts to normal. The drug is easily administered and was well tolerated. Use of this drug in refractory ITP merits further study. Am. J. Hematol. 57:85–86, 1998. © 1998 Wiley-Liss, Inc.

Key words: ITP; refractory; liposomal doxorubicin

INTRODUCTION

Immune or idiopathic thrombocytopenic purpura (ITP) is a relatively common hematologic disorder in adults, likely to be encountered at one time or another by most physicians [1–3]. It is an autoimmune disease in which platelet antibodies cause increased platelet consumption sometimes leading to hemorrhage. Steroids are used as initial treatment in adults, followed by splenectomy. Patients who are refractory to these approaches pose a difficult management problem. While the American Society of Hematology has developed guidelines for the initial management of ITP, there is no consensus on how to manage refractory cases [4–6]. We describe two patients with refractory ITP with severe thrombocytopenia who responded to liposomal doxorubicin after failing multiple prior therapies.

CASE REPORTS

The first patient is a 72-year-old woman who was found to have a platelet count of 3×10^9/L during evaluation of seizures that proved to be secondary to intracerebral hemorrhage. Evaluation, including bone marrow aspiration and biopsy, was compatible with a diagnosis of ITP. Apart from brief increases in platelet counts, she failed to respond to steroids, intravenous immune globulin, splenectomy, and cyclosporine. She did respond to cyclophosphamide (1 g/M^2 every 3 weeks) with a return of platelet counts to normal. Vincristine was given along with cyclophosphamide toward the end of the treatment period, but she ultimately became refractory to this regimen with a decline in platelet count to 4×10^9/L. At this point, liposomal doxorubicin (Doxil) was started (20 mg/M^2 every 2 weeks). After 4 courses of this drug, the platelet count returned to normal levels. The patient remains on this drug at present with a platelet count of 148×10^9/L on last measurement.

The second patient is a 30-year-old man first noted to be thrombocytopenic 11 years ago with typical bone marrow findings of ITP. Prednisone induced a remission that lasted for 5 years. His platelet count subsequently fell to 2×10^9/L and failed to increase with steroids, intravenous immune globulin, splenectomy, and danazol. It finally corrected with vincristine. After a response that lasted 6 years, the platelet count fell to values as low as 1×10^9/L. This time there was no response to steroids, intravenous immune globulin, vincristine, cyclosporine, vitamin C, or intravenous cyclophosphamide (1.5 g/M^2 every 3 weeks). Given this result, the patient was continued on prednisone (starting dose 100 mg daily) in the hopes that this might improve vascular integrity, and started on liposomal doxorubicin (Doxil) 20 mg/M^2 every 2 weeks. Vincristine 1 mg/M^2 was added following

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the first 2 courses. After 4 courses, the platelet count had risen to 60×10^9/L. It is now 150×10^9/L after 6 courses. Prednisone has been tapered and stopped.

Liposomal doxorubicin was well tolerated in both of our patients with no nausea or vomiting. It had modest effects on leucocyte counts and hematocrit levels.

DISCUSSION

Refractory patients comprise about 25 to 30% of patients with ITP [1–3]. The risk of fatal hemorrhage in these patients is about 16% [1]. The first step in management is to search for an accessory spleen. Removal of an accessory spleen may produce a rise in platelet count and improve response to other interventions. There was no evidence for the presence of an accessory spleen in either of our patients.

There is no consensus on how to approach the patient with refractory ITP, mainly because of a lack of solid data [4–6]. Until this situation is rectified, there will continue to be debate about management of these difficult patients. Recently, McMillan suggested a stepwise approach placing various treatments into four levels, based on considerations of side effects and amount of clinical information on their use [7]. Suffice it to say that any classification at this point in time must remain arbitrary and partly subjective.

Our patients had failed a large number of interventions. What is more, both had severe thrombocytopenia with platelet counts below 5×10^9/L. One presented with intracerebral hemorrhage, and the second developed hemorrhagic bullae of the oral mucosa and intractable hematuria. We chose to try a trial of liposomal doxorubicin [8] because of the possibility that it might have an effect on monocytic phagocytes, the cells that mediate thrombocytopenia in ITP by ingesting antibody-coated platelets. The greatest clinical use of liposomal doxorubicin to date has been in the treatment of AIDS-related Kaposi's sarcoma, in which it is generally well tolerated [9], as it was in our patients. If additional experience in cases of refractory ITP is favorable, this drug can be added to the list of effective agents. The cumulative dose is limited by cardiotoxicity so cardiac function must be monitored. Optimal dosing schedule and duration of treatment remain to be determined as does the mode of action.

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