Immune Thrombocytopenia induced by fludarabine succesfully treated with rituximab

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Fludarabine is the most effective chemotherapeutic agent for chronic lymphocytic leukemia (CLL) whether used as a first or second-line therapy. The most common fludarabine toxicities are myelosuppression and immunodeficiency and consequent development of opportunistic infections [1]. Other rare toxicities associated with fludarabine therapy are hemolytic anemia, pure red-cell aplasia, and immune thrombocytopenia [2,3]. We describe a patient with CLL who developed a refractory immune thrombocytopenia following fludarabine treatment that reversed with rituximab.

A 79-year old woman was diagnosed in November 1996 with B-CLL stage A with a lymphocyte count of 68x10^9/L (mature CD5+, CD19+ lymphocytes), hemoglobin 143 gr/L and platelet count 177x10^9/L. She was observed without treatment until progression of disease was detected in March 1998. The patient received treatment with pulses of chlorambucil for one year with good response. However, oral chemotherapy was resumed two years later and stopped in November 2001. Progression was seen again in February 2002, with severe lymphocytosis (100x10^9/L), hemoglobin 122 gr/L and platelet count 78x10^9/L. Fludarabine was started intravenously 5 days every month (25 mg/m^2 per day). The lymphocyte count decreased progressively and the platelet count before the fifth course was 58x109/L. Twenty days after the fifth course of fludarabine the patient was admitted with epistaxis, and skin petechiae. Her lymphocyte count at that time was 4.6x10^9/L, hemoglobin 116 gr/L and platelet count 1x10^9/L (Figure 1). Bone marrow examination showed adequate megakaryocytes. Antiplatelet antibodies were not detected. Standard treatment with oral prednisone 1 mg/kg per day and intravenous immunoglobulin (IvIg) 0.4 gr/kg per day for 5 days was begun (Figure 1). Three weeks later no significant platelet response was observed and 375 mg/m^2 rituximab per week for 4 weeks was begun. The platelet count increased to 29x10^9/L seven days after the first course and a complete resolution of bleeding was observed (Figure 1). At that time, the dose of prednisone was reduced and steroid suspension could be achieved three weeks later. The platelet counts countinued to rise and after four courses of rituximab, the platelet counts achieved levels similar to those detected before starting fludarabine and persisted for at least 1 month (Figure 1).

Our case clearly illustrates that rituximab can be an effective and safe therapy for the induction of remission from refractory fludarabine-associated immune thrombocytopenia. As far as we know, there have been only 3 previous cases of fludarabine-associated immune thrombocytopenia in CLL treated with rituximab [4]. All these patients were refractory to standard treatments and responded at least partially to rituximab. In 2 patients, in concert with our case, the platelet counts showed a rapid increase within the first week of rituximab treatment. It is unclear by what mechanism rituximab might induce remission from fludarabine-associated immune thrombocytopenia. Rituximab has been used successfully in idiopathic thrombocytopenia purpura and other autoimmune diseases [5,6]. Most responding patients showed a rapid improvement in platelet count even within 24 hours of rituximab therapy suggesting other mechanisms different than depletion of antiplatelet antibodies. This rapid increase in platelet count provides support for the speculation that rituximab causes opsonization of B cells that inhibit macrophage Fc receptor function and clearance of IgG-coated platelets.

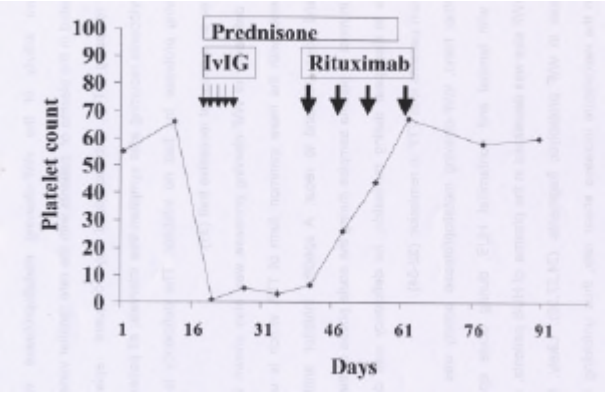

Figure 1

Our experience suggests that it would be reasonable to use rituximab to reverse fludarabine-associated immune thrombocytopenia in patients with CLL, at least in refractory cases. Additional reports will need to be compiled to assess the efficacy and safety of this treatment strategy further.x.

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