Alemtuzumab induced complete remission of autoimmune hemolytic anemia refractory to corticosteroids, splenectomy and rituximab

A 58-year-old man with warm-antibody-mediated autoimmune hemolytic anemia (AIHA) refractory to prednisolone, azathioprine, splenectomy, rituximab and combination chemotherapy, and with unacceptably high transfusion requirement, was treated with alemtuzumab. After a cumulative dose of 883 mg of alemtuzumab, the AIHA remitted completely, with normalization of hemoglobin and transfusion-independence. The major side effect was reactivation of cytomegalovirus, which was controlled with intravenous and oral ganciclovir. This case showed that alemtuzumab might be of use in therapy-refractory AIHA.

We describe the successful treatment of AIHA by the anti-CD52 antibody alemtuzumab in an adult patient refractory to conventional treatment and rituximab.

Case report

A 58-year-old man presented in 2001 with anemia (hemoglobin: 5.4 g/dL, white cell count: 2.9×10^9/L, platelet count: 226×10^9/L). The direct antiglobulin test was positive for IgG and complement (C3b and C3d). Bone marrow examination showed erythroid hyperplasia with no abnormal cellular infiltration. Autoimmune markers, including antinuclear factor antibody, rheumatoid factor, anti-double stranded DNA antibody, anti-cardiolipin antibodies, and antibodies against extractable nuclear antigens, were within normal range or negative. Careful physical examination, and computerized tomographic scan of the thorax and abdomen, did not show any evidence of lymphadenopathy. A diagnosis of AIHA was made. A complete remission was achieved with prednisolone. After treatment for a year, prednisolone was stopped, which was soon followed by disease relapse. A response was obtained again with prednisolone. Despite the addition of azathioprine, he remained corticosteroid-dependent, and reduction of prednisolone dosage was associated with disease deterioration. In May 2004, while on prednisolone 20 mg and azathioprine 75 mg daily, he developed cryptococcal meningitis, which was successfully treated with amphotericin B and flucytosine. A splenectomy was performed in August 2004, which did not result in improvement of transfusion requirement, estimated to be about one unit per week. Prednisolone-induced diabetes mellitus and increase in transfusion requirement to two units per week necessitated a trial of rituximab in October 2004 (375 mg/m²/week×4), which was ineffectual. Two courses of intravenous chemotherapy (cyclophosphamide 500 mg, vincristine 2 mg) were also ineffective. Transfusion requirement became unacceptably high at four to six units per week. In March 2005, alemtuzumab was prescribed (3 mg on the first day, 10 mg on the third day, and 30 mg on the fifth day, and thereafter at 30 mg three times per week) for a total of eight weeks. The transfusion requirement dropped dramatically (Figure 1), with the patient becoming transfusion independent eight weeks afterwards. Alemtuzumab was stepped down to 30 mg weekly for a month, and 30 mg every fortnight for another month. The final total dose of alemtuzumab was 883 mg. Except infusion-related chills, the only significant side effect was reactivation of cytomegalovirus (CMV) after two weeks of alemtuzumab, as detected by polymerase chain reaction (PCR) and pp65 antigenemia.

This was managed with intravenous ganciclovir (5 mg/kg/day), and consecutive negative PCR and pp65 antigen tests were obtained three weeks later. However, on substitution of ganciclovir with acyclovir, CMV reactivated in four weeks, at which point he was treated with oral ganciclovir (900 mg daily). With the achievement of negative PCR and pp65 antigen tests again a week later, ganciclovir was stepped down to 450 mg daily, and stopped upon completion of alemtuzumab therapy. At the latest follow up 16 weeks after cessation of therapy, the patient was asymptomatic and entirely off medication. The direct and indirect bilirubin levels were normal, although the direct antiglobulin test remained positive. His blood counts were hemoglobin: 11.1 g/dL, white cell count: 7.2×10^9/L, and platelet count: 154×10^9/L.

Discussion

Our case showed some interesting observations. Refractory AIHA is an uncommon clinical problem. The use of rituximab in refractory AIHA has been reported in a few adults. Efficacy appeared to be high for AIHA related to cold hemagglutinin disease or an underlying lymphoproliferative disease. However, the response of idiopathic warm-antibody-mediated AIHA was erratic. Rituximab is thus only recommended as a last resort for warm-antibody-mediated AIHA. As shown in this case, rituximab was totally ineffective. In such refractory patients, there were few if any additional treatment options.

We showed in this case that alemtuzumab might be an acceptable treatment for therapy-refractory AIHA. In fact, the use of alemtuzumab has been described in a few cases of autoimmune cytopenias, some in association with underlying B-cell lymphoproliferative disorders. To our knowledge, the treatment of idiopathic AIHA with alemtuzumab had been reported in four patients. Although a remission was reported in one case, the response was delayed at 8 months, during which corticosteroids were continuously prescribed. Hence, a clear-cut response to alemtuzumab could not be documented. Therefore, our patient is the first case of idiopathic AIHA to show a complete response to alemtuzumab alone without other concomitant medication.

Treatment with alemtuzumab leads to lymphoid suppression. Other than bacterial infections, reactivation of cytomegalovirus (CMV) is a significant clinical problem, occurring in 10-66% of patients. We adopted a strategy of regular monitoring and pre-emptive treatment of CMV viremia with ganciclovir. Alemtuzumab was not...
stopped as there was no evidence of organ dysfunction or CMV disease. Furthermore, no significant myelotoxicity was observed during concomitant treatment of alemtuzumab and ganciclovir. Therefore, with appropriate anti-viral therapy, alemtuzumab therapy need not be curtailed.

In conclusion, this case showed that alemtuzumab might be a promising alternative treatment for refractory warm-antibody AIHA, although its role remains to be established by further studies. Its use in other autoimmune cytopenias remains to be evaluated.

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References