To the editor:

Efficacy of alemtuzumab treatment for refractory T-cell large granular lymphocytic leukemia

T-cell large granular lymphocytic leukemia (T-LGL) is a clonal lymphoproliferative disorder representing approximately 2% to 3% of all lymphocytic leukemias. Clonal lymphocytes express CD3, CD8, CD16, and CD5 and share a common rearranged T-cell receptor (TCR). Clinically, the bone marrow, spleen, and liver are extensively infiltrated by LGL, resulting in chronic neutropenia, anemia, and subsequent life-threatening infections. The pathogenesis of these cytopenias is thought to be immune-mediated immunosuppression. Thus, standard therapy utilizes immunosuppressive and/or chemotherapeutic agents. However, none have proven to be universally effective in achieving durable disease control.

References

3. Hamblin TJ, Orchard JA, Ibbotson RE, et al. CD38 expression and immunosuppression. Thus, standard therapy utilizes immunosuppressive and/or chemotherapeutic agents. However, none have proven to be universally effective in achieving durable disease control.

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Neuropathy, anemia, and subsequent life-threatening infections. The pathogenesis of these cytopenias is thought to be immune-mediated immunosuppression. Thus, standard therapy utilizes immunosuppressive and/or chemotherapeutic agents. However, none have proven to be universally effective in achieving durable disease control.
Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen expressed on all lymphocytes: T cells more than B cells and monocytes.\textsuperscript{5,6} Alemtuzumab is approved for use in chronic lymphocytic leukemia and is being evaluated in the treatment of other hematologic malignancies as well as autoimmune diseases. The potential efficacy of alemtuzumab in treatment of T-LGL has not been described previously. Herein, we describe a patient with CD52\textsuperscript{+} T-LGL who, after failing multiple treatment modalities, achieved long-term disease control with alemtuzumab.

A 53-year-old woman presented in January 2000 with anemia, leukopenia, and neutropenia. Signs or symptoms of an associated rheumatologic disorder were not present. Peripheral blood showed lymphocytosis with 98\% of lymphocytes composed of a population of LGL expressing CD2, CD3, CD8, CD16, CD45, and CD57. TCR gene rearrangement studies revealed the presence of a clonal population by polymerase chain reaction (PCR; performed at Mayo Clinic, Rochester, MN). Bone marrow biopsy revealed extensive lymphocytosis with a predominance of large granular T lymphocytes displaying an immunophenotype similar to that observed in the peripheral blood. These findings were consistent with T-LGL. The patient was subsequently treated with a succession of immunosuppressive and/or chemotherapeutic regimens over the course of approximately 20 months as summarized in Figure 1A. She failed to achieve sustained disease control with any of these regimens and remained red blood cell (RBC) and platelet transfusion–dependent throughout her course. In addition, she was hospitalized on 2 separate occasions for neutropenic fevers.

In September 2001, her blood was analyzed for CD52 expression by flow cytometry: over 90\% of the lymphocytes expressed CD52 (Figure 1B). Prior to initiating alemtuzumab therapy, the patient had been untreated for approximately 50 days (more than 1.5 years since her last course of prednisone). During this time, her white blood cell, hematocrit, and platelet counts averaged $0.9 \times 10^9/L$ (0.9 K/µL), 0.25(25\%), and $27 \times 10^9/L$ (27 K/µL), respectively. Peripheral blood mononuclear cells were composed of approximately 80\% lymphocytes (normal = 20\%-40\%) and 10\% granulocytes (normal = 40\%-60\%) (Figure 1B). Alemtuzumab was administered intravenously during the first week as follows: day 1, 3 mg; day 2, 10 mg; day 3, 30 mg. Alemtuzumab was then given in a dose of 30 mg thrice weekly for 6 weeks, once weekly for 3 weeks, and is currently being given in a dose of 30 mg subcutaneously every third week (> 80 weeks). A progression toward normalization of the patient’s peripheral blood counts was observed after alemtuzumab treatment (Figure 1A). Platelets, hematocrit, and absolute neutrophil counts increased significantly and remain stable at $150 \times 10^9/L$ (150 K/µL), 0.4 (40\%), and $1.8 \times 10^9/L$ (1800 K/µL), respectively. Complete blood count and flow cytometry of peripheral blood 80 weeks after alemtuzumab treatment revealed 75\% granulocytes and 11\% lymphocytes: 17\% of lymphocytes expressing CD52 (Figure 1B). The patient has been treated with alemtuzumab for more than 80 weeks with minimal toxicities. She has not required either RBC or platelet transfusions throughout her alemtuzumab treatment, nor has she had any episodes of neutropenic fevers.

To the best of our knowledge, this is the first report to demonstrate long-term successful treatment of T-LGL with alemtuzumab. The dramatic response of this patient suggests the need for a larger scale clinical trial to explore the potential efficacy of alemtuzumab for first-line therapy of T-LGL.

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To the editor:

Rituximab administration following autologous stem cell transplantation for multiple myeloma is associated with severe IgM deficiency

Clonotypic B cells are frequently isolated from the peripheral blood of patients with multiple myeloma (MM). These clonotypic B cells may be the clonogenic cells of MM. We have hypothesized that rituximab, a chimeric CD20 monoclonal antibody, may be a useful maintenance therapy in MM after autologous hematopoietic stem cell transplantation (HSCT). The rationale was that CD20 antibody would deplete the clonotypic and, possibly, clonogenic B cells, in the setting of major malignant plasma cell eradication, to reduce the risk of disease relapse. Furthermore, CD20 has been shown in recent studies to be expressed on malignant plasma cells in up to 20% of patients with MM. CD20 antibody has previously been used with limited success to treat patients with MM in a phase 2 study.

Autologous hematopoietic stem cells (HSCs) were mobilized with cyclophosphamide (3 g/m²) and granulocyte colony-stimulating factor (G-CSF; 10 μg/kg per day) from patients with MM. Two to 3 weeks after stem cell collection, high-dose melphalan (200 mg/m²) was administered intravenously followed 24 hours later by the infusion of at least 2 × 10⁸/kg CD34⁺ cryopreserved autologous stem cells. Rituximab infusion (375 mg/m²) was started on day +30. Each patient received one antibody infusion every 3 months for 2 years or until disease progressed. All patients continued on monthly zoledronate (4 mg) and did not receive any other antimalyeloma treatment.

A total of 10 patients have been treated. However, only the 7 patients who have had posttransplantation follow-up periods of more than 12 months were evaluated. One of the 3 patients with follow-up periods of less than 12 months has achieved a complete remission (CR; defined by negative serum protein electrophoresis and immunofixation electrophoresis) and the other 2 patients achieved a partial remission. The immunoglobulin recovery and incidence of infections in this group of patients were compared to 6 patients with MM who have undergone an autologous stem cell transplantation but without the administration of rituximab.

The total normal immunoglobulin M (IgM) level in all 7 patients was severely depressed following rituximab administration (Figure 1A). Unlike patients with non-Hodgkin lymphoma who received rituximab infusions after autologous stem cell transplantation in which IgG recovery was depressed, the immunosuppression in patients with MM was observed primarily in IgM and only variably in IgG and IgA (data not shown). The IgM immunosuppression was prolonged and consistent, being observed in all 10 treated patients, regardless of the disease status after transplantation. In contrast, the control group showed normalization of the total IgM levels by 3 months after transplantation. Two patients treated with rituximab received pneumococcal vaccines 12 months after transplantation and neither developed any IgG response to the vaccine. The data indicate that rituximab infusion following autologous transplantation for MM severely impaired B-cell immune reconstitution.

The clinical significance of the IgM immunodeficiency was next examined. Six of the evaluated 7 patients developed moderate to severe infection during the first 12 months after initiation of rituximab infusion. The cumulative infection episodes in these 6 patients are shown in Figure 1B. There were a total of 23 episodes of infection: 21 episodes of pneumonia and 2 episodes of sepsis (one pneumococcus and one Pseudomonas). A patient died in CR due to pneumonia. In contrast, only one episode of pneumonia was observed in the control group during the same follow-up period. Therefore, the IgM immunodeficiency probably predisposed the patients to infection.

Of the 7 patients who have had more than 12 months of follow-up periods, 4 had disease refractory to standard induction chemotherapy. Of all the 10 patients treated, 6 achieved CR (2 were in CR before treatment, 2 achieved CR 3 months after treatment, and 2 achieved CR 6 months after starting rituximab). All 4 patients with refractory MM (all had a follow-up of more than 12 months) achieved CR, one before and 3 after starting rituximab. One of the refractory patients has since relapsed, one died of pneumonia 12 months after transplantation, and the other 2 have remained in CR 12+ and 18+ months after transplantation. With a follow-up of 29 months after transplantation, the progression-free survival was 56.5% and the overall survival 71.4%.

Rituximab infusion after autologous stem cell transplantation for MM is therefore associated with severe IgM immunodeficiency and an increased risk of infection. Further works are needed to determine the antitumor activities of rituximab in MM.

Figure 1. IgM levels and infection risk. (A) Mean total IgM levels before and after starting rituximab infusions ( ), showing significantly lower levels at the 3-, 6-, 9-, and 12-month intervals when compared with those who did not receive rituximab ( ) after autologous transplantation. NS indicates not significant; *, P < .02; **, P < .001; and ***, P < .0001. (B) The cumulative episodes of infections in the rituximab group ( ) and the control group ( ), showing that there was an obvious excess of infective episodes in patients who received rituximab.
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