Successful treatment of pure red cell aplasia with rituximab in patients with chronic lymphocytic leukemia

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Pure red cell aplasia (PRCA) is a rare complication in patients with chronic lymphocytic leukemia (CLL). It is characterized by reticulocytopenia and by an absence of red cell precursors in the bone marrow. Unlike autoimmune hemolytic anemia, which is characterized by an increased number of reticulocytes, positive Coombs test findings, and a high serum level of lactate dehydrogenase. Two patients with B-cell CLL are reported to have developed PRCA, one while on chemotherapy with fludarabine and one seeking treatment for de novo PRCA. Both responded dramatically to therapy with monoclonal antibody rituximab (Rituxan) in a short period of time and continued to be transfusion-independent. These are the first 2 reported patients for whom rituximab treatment for PRCA in CLL was successful, and this treatment deserves further investigation. (Blood. 2002;99:1092-1094)

Study design

Patient 1

The first patient was a 79-year-old man who sought treatment for severe anemia in April 2000. He had an elevated white blood cell (WBC) count of \( 25 \times 10^9 /L \) with 80% lymphocytes. A diagnosis of B-cell CLL was made based on flow cytometry analysis showing 90% CD20 and 97% CD5 positivity. Bone marrow aspiration and biopsy specimen showed a diffuse pattern of lymphocytic involvement, and chromosomal analysis revealed trisomy 12. His hemoglobin level dropped to 7.0 g/dL, and he required blood transfusions every 3 weeks or so. There was no evidence of hemolysis by virtue of negative Coombs test results, normal serum LDH level, and reticulocyte count of 0.1% with near-absent red cell precursors in the marrow. He had normal serum vitamin B12 and folate levels, elevated ferritin level, normal platelet count, and no evidence of blood loss. In addition, human parvovirus B19 immunoglobulin (Ig)G and IgM findings were negative, and his erythropoietin level was elevated at 647 IU/L.

He received cyclosporin A to maintain serum level of more than 100 ng/mL. After 4 weeks, prednisone (40 mg/d) was added because treatment elicited no response thus far. His course afterward was complicated by the development of steroid-induced diabetes mellitus and rising WBC counts up to \( 75 \times 10^9 /L \), 4 months after he initially sought treatment, and by transfusions every 3 weeks or so. At that point (September 2000), intravenous immunoglobulin was initiated at 1 g/kg per day for 2 days, again without much change in his anemia. In October 2000, 6 months after cyclosporin–prednisone therapy, rituximab was administered at 375 mg/m² per week for 8 consecutive weeks, based on some data on its efficacy in CLL with AIHA and based on results in our second patient. He tolerated this treatment extremely well and did not have side effects. His WBC count...
was $45 \times 10^9/L$, and that decreased in a week to $12 \times 10^9/L$ and to $3.6 \times 10^9/L$ in only 2 weeks. His hemoglobin count was 8.1 g/dL during the second week of rituximab therapy, and he needed 2 U blood. This was the last transfusion he needed. Dramatically, his reticulocyte count rose to 2.5%, and by the eighth week on rituximab, his hemoglobin count was 12.1 g/dL, and for the first time in 8 months he did not need a transfusion. Repeat bone marrow aspiration and biopsy specimen showed resolution of the PRCA with normal maturation of his erythroid series and near resolution of lymphocytic infiltration. At last follow-up (August 2001), his WBC count was $6.1 \times 10^9/L$, his lymphocyte count was $2.6 \times 10^9/L$, his hemoglobin count was 13.5 g/dL, and his platelet count was $170 \times 10^9/L$, indicating continuing remission of CLL and PRCA.

**Patient 2**

The second patient is a 47-year-old woman with a 7-year history of B-cell CLL, initial WBC count of $43 \times 10^9/L$, hemoglobin level of 13.5 g/dL, and normal platelet count (findings in January 1994), and clinically she remained in stage 0 disease. In late 1999, her WBC count began to rise rapidly and reached $160 \times 10^9/L$ in February 2000 with a high β2 microglobulin level (2.4 mg/dL). Fludarabine was administered at that time at $25 \text{mg/m}^2$ day for 5 days every 3 to 4 weeks. After 5 cycles, her WBC count was $22 \times 10^9/L$, and her hemoglobin level dropped to 7.1 g/dL, and she became transfusion-dependent. Her reticulocyte count was 0.1%, and she had no evidence of hemolysis based on negative direct Coombs test, normal serum LDH level, and normal bilirubin level. Vitamin B12 and folate levels were normal, ferritin level was elevated, and human parvovirus B19 titer were negative. She declined bone marrow biopsy at that time. In July 2000, after 6 cycles of fludarabine therapy, her WBC remained slightly elevated at $14 \times 10^9/L$ with 80% lymphocytes, normal platelet count, and blood transfusion dependence in spite of erythropoietin (Procrit, Ortho Biotech Products, Raritan, NJ) injections for more than 4 months. Anemia could not be attributed to overcrowded bone marrow because before therapy with fludarabine, her WBC was $160 \times 10^9/L$. At that time her hemoglobin level and reticulocyte count were normal, and now her WBC count is only $14 \times 10^9/L$, indicating major shrinkage of the lymphocyte population. Given that fludarabine failed to achieve complete response and that there was a possibility of inducing immune modulation to change her transfusion dependency—combined with reports of rituximab inducing responses in patients with AIHA and CLL—rituximab was tried as a consolidation therapy 6 weeks after her last cycle of fludarabine treatment. The patient tolerated rituximab (375 mg/m² per week for 8 weeks) extremely well and had no side effects. Her WBC count dropped to approximately $5 \times 10^9/L$ with 50% lymphocytes. More important, her reticulocyte count increased gradually from 0.1% to approximately 10% by the eighth week of rituximab therapy, and she became transfusion-independent after the fourth week of treatment. As of August 2001, a year after the initiation of rituximab treatment, her hemoglobin level is normal at $14.2 \text{ g/L}$, WBC is $2.5 \times 10^9/L$, absolute lymphocyte count is $1.2 \times 10^9/L$, platelet count is $209 \times 10^9/L$, and reticulocyte count is 2.3% (Figure 1).

**Results and Discussion**

As stated, anemia in patients with CLL can be attributed to many factors, notably overcrowding of the marrow with leukemia cells, hypersplenism, and auto-immune hemolysis. Rarely is it attributed to PRCA. The pathogenesis of the latter is not well understood, but abnormal Tγ cells were found to inhibit the growth of erythroid progenitor burst-forming and colony-forming units. These Tγ cells included IgG-Fc receptor, and levels were higher in patients with CLL-PRCA than in patients with stage III CLL. In addition, the Tγ cells decreased markedly with effective therapy for PRCA. Rituximab is a monoclonal antibody designed to target the CD20 antigen on B cells, inducing apoptosis. Small uncontrolled trials and case studies have reported the use of rituximab for the treatment of patients with AIHA. PRCA can coexist with AIHA in some patients, although both our patients had no evidence of hemolysis. To our knowledge, this is the first published report of rituximab use for the treatment of PRCA in CLL. The article by Zecca et al of AIHA and PRCA in an infant reports one of the rare combinations in the same patient. Even though the factors are different than they are for our 2 patients with CLL and PRCA, it is interesting that the infant responded to rituximab as well after only 2 weekly treatments. Perhaps this confirms that the rituximab mechanism of action is that of an immune modulatory effect. A note of caution: although our patients tolerated therapy well, cytokine release syndrome and tumor lysis have been reported after the administration of rituximab to patients with CLL whose lymphocyte counts were elevated. Rare cytokopenias have been observed, and PRCA associated with rituximab therapy developed in a single patient with chronic human parvovirus B19 infection.

T-cell dysfunction has been proposed as the etiology of PRCA in patients with CLL. Our results using rituximab, which primarily depletes B cell stores, challenges that idea and points to a possible role for B cells’ dysfunction as well. Whether rituximab also
induces an immune modulatory effect on those Tγ cells remains to be seen. The other issue is the addition of rituximab, in our second patient, after fludarabine therapy. Chemotherapy such as chlorambucil may select for those abnormal Tγ lymphocytes and may increase their number, inducing PRCA. It remains a mystery how rituximab, which depletes B cells, cleared PRCA after fludarabine therapy. Perhaps B cells are the final messengers by which Tγ cells relay the message.

Clearly, there is still a lot to be learned on this subject, and we are far from a breakthrough, but at least we have documented positive results using rituximab for treating PRCA in patients with CLL. Further investigation is definitely warranted.

References


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