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

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**Introduction**

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 × 10⁹/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 human parvovirus B19 IgM findings during de novo presentation without any prior therapy and one during therapy with fludarabine (Fludara; Berlex, Richmond, CA), a drug that can be associated with autoimmune hemolytic anemia (AIHA). The first patient did not respond to known therapeutic measures for 6 months and then responded dramatically to rituximab in a short period of time. After the second patient completed fludarabine therapy, rituximab treatment was begun and produced a dramatic response in PRCA and a normalization of blood counts in a short period of time. To our knowledge, this is the first published report of the use of rituximab for the treatment of PRCA in patients with CLL, and it warrants further investigation. Recently, an infant with AIHA and PRCA was reported to have responded well to rituximab at 375 mg/m² weekly for two weeks and became transfusion-independent.

We describe 2 patients with B-cell CLL and PRCA, one detected during de novo presentation without any prior therapy and one during therapy with fludarabine (Fludara; Berlex, Richmond, CA), a drug that can be associated with autoimmune hemolytic anemia (AIHA). The first patient did not respond to known therapeutic measures for 6 months and then responded dramatically to rituximab in a short period of time. After the second patient completed fludarabine therapy, rituximab treatment was begun and produced a dramatic response in PRCA and a normalization of blood counts in a short period of time. To our knowledge, this is the first published report of the use of rituximab for the treatment of PRCA in patients with CLL, and it warrants further investigation. Recently, an infant with AIHA and PRCA was reported to have responded well to rituximab at 375 mg/m² weekly for two weeks and became transfusion-independent. 
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 $b_2$
microglobulin level (2.4 mg/dL). Fludarabine was administered at that time
at 25 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
folic acid were normal, ferritin level was elevated, and human parvovirus
B19 titers 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/m$^2$ 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 g/dL, 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 T$\gamma$ cells were found to inhibit the growth of erythroid
genitor burst-forming and colony-forming units. These T$\gamma$ cells
were higher in patients with CLL–PRCA than in patients with stage III CLL. In
addition, the T$\gamma$ 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 uncon-
trolled 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 a 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
unusual responses in patients with AIHA and CLL—rituximab was tried as a
consolidation therapy 6 weeks after her last cycle of fludarabine treatment.

Figure 1. Hemogram and treatment sequence of patient 2. Arrow ( ▼ ) represents
fludarabine cycle, and ( ▲ ) represents rituximab treatment.
induces an immune modulatory effect on those T_/H9253_ 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 T_/H9253_ 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 T_/H9253_ 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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