CONCISE REPORT

High-Dose Methotrexate With Leucovorin Rescue: Effectiveness in Relapsed Hairy Cell Leukemia

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Six patients with relapsed hairy cell leukemia after splenectomy were treated with high-dose methotrexate and leucovorin rescue. Five patients had objective responses as determined by improved blood counts. In two of them, the response has continued for more than 14 and 44 months.

Hairy cell leukemia is a condition usually characterized by splenomegaly without adenopathy, pancytopenia, and recurrent infections. The circulating malignant cells frequently show prominent cytoplasmic projections and in most cases they stain positively for acid phosphatase and are tartrate-resistant. The bone marrow and spleen show a typical infiltration by hairy cells.

Generally, splenectomy is applied as the first line of treatment. Indications for treatment are severe granulocytopenia, severe thrombocytopenia, requirements for frequent blood transfusions, recurrent infections, or spleen infarction.

There is one large study which reports that splenectomy does not prolong survival in patients beyond the age of 60 or in subjects with symptoms for more than 12 months, with a spleen less than 4 cm under the costal margin.

Following splenectomy, there is prompt hematologic improvement in about 50% of the cases. About one third to two thirds of post-splenectomy patients will require additional therapy because of no improvement or progressive disease. The median time to relapse after splenectomy is about 2 1/2 months for partial responders and 16 months for complete responders. There is no agreement about the best second line of therapy. In addition, it is very difficult to decide at what time treatment should be initiated. Although there are reports on beneficial effects of aggressive chemotherapy, this is often withheld because of the danger of severe and long-lasting pancytopenias.

Promising results with low dose alkylating agents and alpha interferon in small patient groups have been recently reported.

This report describes the results of high-dose methotrexate (MTX) followed by leucovorin rescue in six patients with relapsed hairy cell leukemia after splenectomy.

MATERIALS AND METHODS

Five males and one female were treated with high-dose MTX and leucovorin rescue. The clinical and hematologic features are summarized in Table 1. All had previously undergone splenectomy at one to 12 months after their first symptoms and one to 42 months before MTX therapy. The diagnosis of hairy cell leukemia was based on cytologic and histologic examination of the bone marrow and spleen.

The acid phosphatase stain of the hairy cells was positive in all six patients, while they were tartrate-resistant in five of six. In all cases, there was evidence of progressive disease prior to the initiation of MTX treatment. Progressive disease was defined by malaise and weight loss (patients No. 2, 4, 5, and 6), infectious complications plus or minus progression of granulocytopenia (patients No. 1, 3, and 6), or rapidly increasing thrombocytopenia (patients No. 1 and 3).

In patient No. 5 the disease was dominated by the development of ascites and extensive abdominal lymph node masses (histologically proven hairy cell leukemia by laparotomy).

MTX (2 g/m²) was given intravenously over one hour with forced diuresis initiated at 12 hours before starting methotrexate therapy. Alkalization of the urine was achieved with sodium bicarbonate given intravenously. Rescue with leucovorin was begun at 24 hours in a dose of 25 mg/m² and repeated at six-hour intervals during at least 48 hours until MTX serum levels had fallen below $1 \times 10^{-8}$ mol/L. These courses were repeated every four to six weeks.

As parameters of response, we used absolute granulocyte and platelet counts and Hb levels. It is of interest to mention that maximum values were noted between two and three months after discontinuation of all MTX therapy, although first signs of improvement were seen after the second course. Furthermore, the percentage of hairy cells in the bone marrow as well as the presence of hairy cells in the blood were evaluated.

RESULTS

The effects of treatment are shown in Table 1. Four patients showed a significant rise in platelet values, while four exhibited modest improvement in their granulocyte counts and four had a notable increase in hemoglobin level. However, in no case did the hairy cells disappear completely from peripheral blood and marrow. Of the four responding patients who are still alive, three showed a decrease in the percentage of hairy cells in the marrow and in patient No. 6 the marrow did not reflect improvement in hairy cell counts.

In two patients (No. 2 and 5), the response has continued for longer than 44 and 14 months, although in patient No. 5, abdominal lymph node masses remained present on computed tomography (CT) scan without ascites. Patient No. 4 had a relapse 3 months after the last methotrexate course and was placed on other chemotherapy. Patient No. 6 was stable at the time of evaluation and in good clinical condition without infectious complications, at a granulocyte and platelet level slightly better than before MTX therapy, but the follow-up is still short.

So far, two patients have died, both early during MTX.
treatment. Of these, one (No. 1) died of extensive candidiasis and the cause of death in patient No. 3 was a myocardial infection after his second course of MTX, to which he had shown a good objective response. Myelosuppression was in no case severe. No patient showed granulocyte counts lower than the initial values at any time during treatment and platelet counts never decreased below the level of $30 \times 10^9$ per liter, except in patient No. 3 who presented with a thrombopenia of $12 \times 10^9$ per liter.

**DISCUSSION**

High-dose MTX treatment followed by leucovorin rescue produced good objective partial responses in five of six previously splenectomized patients with progressive hairy cell leukemia. The two patients (No. 2 and 5) in whom this treatment resulted in lasting responses (ie, $44^\circ$ and $14^\circ$ months) started with the highest absolute neutrophil counts, which might indicate a better prognosis. This form of treatment is well tolerated. It is of particular interest that the treatment was not associated with obvious myelosuppression, as it is known that these patients have limited bone marrow tolerance to cytotoxic therapy. No serious problems of nephrotoxicity or gastrointestinal toxicity were observed.

Compared with other reports on intensive treatment for hairy cell leukemia, we believe that therapy with high-dose MTX with leucovorin rescue is quite safe, is associated with minimal toxicity, and therefore may have a place in the treatment of hairy cell leukemia. Based on the data presented, the treatment of more patients with this modality is warranted. Because of the considerable expense of high-dose MTX, the evaluation of intermediate dosages of the drug would seem to be of interest.

**REFERENCES**

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