TREATMENT OF HAIRY CELL LEUKEMIA (LEUKEMIC RETICULOENDOTHELIOSIS) II. CHLORAMBUCIL THERAPY IN POSTSPLENECTOMY PATIENTS WITH PROGRESSIVE DISEASE

By Harvey M. Golomb and Uri Mintz

Four postsplenectomy patients with progressive hairy cell leukemia were treated with daily low doses of an alkylating agent (chlorambucil, 4 mg). An objective response, measured by improvement in blood counts in four patients as well as decreased bone marrow involvement on core biopsy in three patients, could be documented within 6 mo. It is important to identify the postsplenectomy patient with progressive disease as early as possible in order to initiate low-dose single agent chemotherapy and to have the time necessary to effect an objective response.

ALTHOUGH hairy cell leukemia was first recognized as a distinct clinical-pathologic entity in 1958, treatment strategies have only recently been formulated. Retrospective analyses have suggested that splenectomy is beneficial and that chemotherapy is harmful. Two reports, however, suggested that seriously ill patients can benefit from aggressive combination chemotherapy.

The manifestations of hairy cell leukemia result from leukemic infiltration of two organ systems: (1) infiltration of the red pulp of the spleen by hairy cells, which leads to hypersplenism and (2) infiltration of the bone marrow, which leads to decreased production of bone marrow elements and peripheral blood cytopenia(s). The hypersplenism can be corrected in the majority of patients by splenectomy. However, approximately 27% of the patients subsequently have progressive disease in the bone marrow, which manifests itself either by a leukemic phase with various associated cytopenias or by progressive pancytopenia. The treatment strategy for these latter patients is the subject of this report.

MATERIALS AND METHODS

Between January 1, 1974 and June 30, 1978, 44 patients with hairy cell leukemia were identified and entered into a clinical study. The diagnosis was verified by cytochemistry studies, bone core biopsy, or spleen tissue morphology or a combination of these in each case. Of the 44 patients, 26 underwent splenectomy either before consultation at our institution (14 patients) or upon our recommendation (12 patients). Nineteen of these patients required no further therapy, but the other 7 developed evidence of progressive disease and needed treatment. Of these 7 patients, 2 died at other institutions without being treated, 1 died at our institution of pulmonary insufficiency secondary to hairy cell infiltration 3 days after combination chemotherapy was initiated, and 4 patients were treated at our institution at the first indication of advancing disease. Treatment consisted only of administration of chlorambucil, 4 mg/day...
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Fig. 1. (A–D) The clinical course for patients 1–4 is shown graphically. The date of bone core biopsy is indicated; the results are given in Table 1. Percentage of granulocytes is shown in parentheses.

(Fig. 1), which was decreased to 2 mg/day as a response could be documented. Allopurinol, 300 mg daily, was started prophylactically together with chlorambucil administration.

RESULTS

The characteristics and clinical course of the four patients* who received chemotherapy are shown in Fig. 1 (A–D). All four were postsplenectomy at the time when the clinical course was judged to be deteriorating. Deterioration is defined as a steadily increasing white blood cell (WBC) count (15,000/cu mm or more) with the majority hairy cells, or a steadily decreasing hematocrit that drops below 30% without blood loss, or a platelet count that decreases to less than 50,000/cu mm. Patients 1–3 were in the leukemic phase when chemotherapy was begun. Although patients 1 and 2 had an increasing WBC count postsplenectomy, with hairy cells predominating, there was little decrease in either the hematocrit or

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Table 1. Results of Sequential Bone Core Biopsies

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Date of Bone Core Biopsy</th>
<th>Percent Cellularity</th>
<th>Percent Hairy Cells</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7/72</td>
<td>40</td>
<td>50</td>
<td>Moderate fibrosis</td>
</tr>
<tr>
<td></td>
<td>5/77</td>
<td>20</td>
<td>&lt;5</td>
<td>No fibrosis, normal elements</td>
</tr>
<tr>
<td>2</td>
<td>3/76</td>
<td>35</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/78</td>
<td>35</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11/77</td>
<td>20</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/79</td>
<td>10</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3/77</td>
<td>70</td>
<td>50</td>
<td>Regenerating, clusters of normal elements</td>
</tr>
<tr>
<td></td>
<td>10/77</td>
<td>85</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10/78</td>
<td>50</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

platelet count. Patient 3, however, had significant anemia as well as the leukemic phase of the disease upon being admitted to our institution. Patient 4 remained leukopenic postsplenectomy, but became increasingly thrombocytopenic and anemic.

Bone core biopsies were performed on four patients before initiation of chlorambucil chemotherapy and during the period of hematologic response; the results are shown in Table 1.

The institution of chlorambucil therapy in patient 1, 9 yr postsplenectomy, led to such a dramatic reversal in the course of the disease that his blood counts were normal in May 1978; a bone core biopsy in May 1977 had shown few hairy cells.

Patient 2 began chlorambucil treatment 2 mo after splenectomy because of persistent anemia as well as a persistent leukemic phase of the disease. Within 1 yr, her hematocrit had returned to normal and her WBC count was stabilized at 5700/cu mm. Her platelet count remained high, but the percentage of granulocytes never rose. The bone marrow showed a slight decrease in the percentage of hairy cells (Table 1). This patient died of pseudomonas pneumonia and sepsis within 2 days after an admission to her local hospital; she is the only patient treated with chlorambucil who has died and may represent a treatment-related death.

Patient 3 had severe anemia, thrombocytopenia, and the leukemic phase of the disease approximately 10 yr postsplenectomy. Within 7 mo after initiation of chlorambucil therapy, his hematocrit had returned almost to normal without transfusions, his WBC stabilized at 3400/cu mm with few hairy cells, and his platelet count increased to 221,000/cu mm. Although his bone core biopsy in February 1979 showed no objective improvement from November 1977, his hematocrit and platelet count were within normal limits. He remains asymptomatic and is a fully active practicing physician.

Patient 4 was anemic 3 mo after splenectomy. Three months later (10/77), he had become thrombocytopenic as well. A bone core biopsy at this time (Table 1) showed more cellularity and a higher percentage of hairy cells than a presplenectomy specimen. The patient was started on chlorambucil and given supportive red blood cell transfusions for 5 mo. Seven months after the start of chemotherapy, his hematocrit was stable and his platelet count had improved. By 10 mo, his hematocrit and platelets were almost normal; his WBC count remained under 3000/cu mm, but there have been few hairy cells. A repeat bone core biopsy in
October 1978 showed decreased cellularity, with only about 40% hairy cells; there were many clusters of normal elements, suggesting a regeneration of the marrow.

**DISCUSSION**

The results in our four patients suggest that postsplenectomy patients with hairy cell leukemia who have either the leukemic phase of the disease or increasing pancytopenia due to bone marrow replacement can benefit from chemotherapy with low doses of an alkylating agent. The period from beginning treatment to response is approximately 6 mo. It is important to identify promptly a declining state postsplenectomy so that single-agent chemotherapy can be begun and its beneficial effects realized in time.

Until the past several years, chemotherapy was reported as being of little benefit in the treatment of hairy cell leukemia and in some reports even as being harmful because it produces myelosuppression without remission. Two reports of prolonged remission following intensive chemotherapy suggest that some patients with hairy cell leukemia can benefit from therapy with cytotoxic agents. The first report that described improvement of a hairy cell patient with androgen therapy was published in 1961; the second report of success was not until 1978. Only the most recent patient was documented as having progressive disease after an initial good response to splenectomy; the response took 4 mo to develop. Besa and Gardner reported on a patient who failed to respond to splenectomy and 8 mo of androgen therapy, but did respond during the third month of therapy with etiocholanolone and prednisolone; this patient was alive and well 2 yr after the cessation of 11 mo of therapy. A patient reported by Moore et al. received no benefit from splenectomy and had a white blood cell count of 40,000/cu mm; intensive leukopheresis decreased the WBC count to approximately 5000/cu mm, and the anemia and thrombocytopenia improved.

From our experience of the past several years, we have evolved a strategy for the sequential care of each patient with hairy cell leukemia. At diagnosis, one must begin to determine the pace of the disease. Some patients require no therapy; they are usually elderly and have minimal splenomegaly. When there is evidence of increasing symptomatic splenomegaly (cytopenia, discomfort, infarction), splenectomy is indicated. Approximately 27% of patients have signs of progressive disease after splenectomy and require further treatment. Our study suggests that chemotherapy with a single alkylating agent is indicated and can result in reversal of the cytopenia and of the involvement of the bone marrow. Our patients have required no further therapy as of January 1979. If these patients fail, the use of androgen therapy, intensive leukopheresis, and combination chemotherapy remains to be tested.

**ACKNOWLEDGMENT**

We thank Dr. Stanley Yachnin for making patient 1 available for study.

**REFERENCES**

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Treatment of hairy cell leukemia (leukemic reticuloendotheliosis) II. Chlorambucil therapy in postsplenectomy patients with progressive disease

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