Intensive Chemotherapy of Hairy Cell Leukemia in Patients With Aggressive Disease

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Seven patients with hairy cell leukemia were treated by intensive chemotherapy because they were considered to have a progressive disease and a poor short-term prognosis. The mean age was 47 years (range, 36 to 58). Six of seven patients had prior splenectomies with minor or transient hematologic responses. One patient had no spleen enlargement. The seven patients had never received any cytotoxic drugs and had prolonged granulocytopenia (< 300/μL) with recurrent, severe infectious episodes. Chemotherapy included Rubidazeon (zorubicine hydrochloride) 450 mg/m² on day 1, arabinosyl cytosine 200 mg/m²/d from day 1 to day 5, and cyclophosphamide, 2,000 mg/m² on day 5. Responses were assessed through examination of repeat bone marrow biopsy specimens and blood counts. A complete response was defined as normal blood counts with the disappearance of hairy cell infiltration and fibrosis on the bone marrow biopsy specimens. A partial response was defined as normal blood counts with persistence of leukemic cells in the bone marrow. Three patients achieved a complete response, and one patient had a partial response. Three patients died of infectious complications during induction chemotherapy. For the responding patients, the mean duration of aplasia was 37 ± 5 days. Follow-up for the responding patients has been 44+, 24, 32+, and 23+ months. One patient with a complete response died while on maintenance therapy. We conclude that complete and prolonged histologic remission of hairy cell leukemia can be obtained with intensive chemotherapy. The toxicity of chemotherapy is such, however, that progressive disease after splenectomy needs to be more clearly defined.

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THE DEVELOPMENT of hairy cell leukemia is usually insidious and includes as main symptoms pancytopenia and splenomegaly, with the presence of hairy cells in the peripheral blood and bone marrow.1-5

The median survival in a large series is about four years.3,4,7 The disease can be remarkably indolent; some patients with minimal cytopenia and absent or minor splenomegaly will not require any specific treatment. Conversely, patients with splenomegaly will clearly benefit from splenectomy in terms of survival, as shown by several studies.3,4,10,11 Usually, splenectomy leads to partial or complete recovery of hemoglobin, platelet, and granulocyte levels in 50% to 90% of reported cases.7,10,12,13 Some patients, however, do not respond or respond poorly to surgery and seem to have a poor prognosis.3,13 This led us to propose a specific treatment aiming to cure the underlying malignant condition.14

Low doses of chlorambucil have induced responses in which platelet and hemoglobin levels have increased but remission was not complete.15,16 There appeared to be little benefit on the number of circulating granulocytes, and the patients remained at risk of developing a life-threatening infection.16 Other drugs alone or in combination, such as vinca alkaloids,6,7,17,18 alkylating agents,5,7 glucocorticosteroids,1,2,3,7 phosphorus-32,1,2 and androgens18,19 have been tested without any convincing effect.14,20 More recently, Quesada et al reported excellent responses to alpha interferon in patients with hairy cell leukemia who had slow progressive disease.21 There are very few reports concerning high dose or combination chemotherapy, but some complete remissions have been obtained.22-27

Between February 1980 and January 1984, 101 patients with hairy cell leukemia were followed in our hematologic department. Of this group, seven patients with severe bone marrow insufficiency were treated with intensive chemotherapy; the results of that study are reported here.

MATERIALS AND METHODS

Patients

The characteristics of the seven patients are shown in Table I. The mean age was 47 years (range, 36 to 58), their Karnofsky performance status was greater than 70, and none had previously received any cytotoxic agent. The time interval between diagnosis and initiation of chemotherapy (CT) ranged from four to 72 months. Three patients (No. 1, 2, and 4) had less than a nine-month interval between diagnosis and treatment.

The seven patients were selected to receive chemotherapy because they were considered to have a poor short-term prognosis: prolonged cytopenia, mainly granulocytopenia with recurrent infectious episodes, and anemia requiring red cell transfusions. One patient had neither spleen enlargement nor splenic sequestration and was not treated surgically. Chemotherapy was indicated in that particular patient because of rapidly progressive granulocytopenia, anemia, and severe recurrent infectious episodes. The six other patients had undergone splenectomy 2, 4, 6, 24, and 60 months before CT; four of them had minor or transient hematologic responses following splenectomy, two patients had responses that would meet Catovsky's criteria3 for complete response. These lasted for 20 and 56 months and were followed by relapse of granulocytopenia and anemia in both cases. Six patients were anemic before CT, five of them needing...
monthly red cell transfusions. Five patients had platelet counts of less than 100 x 10^9/L; in three cases, thrombocytopenia was severe, but none of them had severe bleeding. Severe neutropenia was constant in our patients, equal to zero before CT in four cases. All patients had had infectious symptoms before treatment. Most of them were undocumented and were treated with empiric antibiotherapy.

Five patients had previous treatment. Four of them had received methyl prednisolone with mild transient improvement of blood counts, and the fifth received lithium carbonate without any effect.

Chemotherapy

The seven patients were hospitalized in our hematology unit. They all received prophylactic oral nonabsorbable antibiotics and oral Fungizone.

They received support therapy with red cells, platelet units, and granulocyte transfusions when needed. One single course of induction regimen was administered to the seven patients, combining Rubidazone (zorubicine hydrochloride), 450 mg/m^2 of body surface area IV on day 1, arabinosyl cytosine, 200 mg/m^2/d in continuous IV infusion from day 1 to day 5, cyclophosphamide, 2,000 mg/m^2 IV on day 5. The first two patients received oral 6-mercaptopurine 200 mg/m^2/d from day 1 to day 5. This drug was withdrawn for the subsequent five patients because of vomiting during the five-day treatment.

We initially planned to treat the patients after induction therapy with maintenance CT consisting of monthly cycles combining arabinosyl cytosine, 100 mg/m^2 every 12 hours subcutaneously from day 1 to day 5, vincristine, 1.5 mg/m^2 IV on day 1, and cyclophosphamide, 500 mg/m^2 on day 1 IV. Because the indications for maintenance therapy are not definite and considering the high toxicity of this maintenance (see toxicity), we stopped the maintenance program after the first two patients.

Response Criteria

Our criteria for response were hematologic and histologic, assessed on repeated bone marrow biopsy specimens embedded in epoxy according to the technique described by Bryon. Patients had a bone marrow biopsy before therapy, then at one and three months after the onset of treatment. Subsequent biopsies were performed at least once a year. Complete remission was defined as hemoglobin level >12 g/dL, a platelet count of >150 x 10^9/L, a neutrophil count of >1.5 x 10^9/L in peripheral blood, with normal cellularity, complete disappearance of hairy cell leukemic infiltration, and no fibrosis on bone marrow biopsy. A partial response was defined as persistence of hairy cells and fibrosis with normal myeloid repopulation in the bone marrow associated with normalization of hematologic variables in the peripheral blood as described.

RESULTS

Of the seven patients treated, four had responses (patients 1, 2, 3, and 6); three achieved complete remission; and one patient (No. 6) had a partial response according to our criteria. Response duration for these patients is 44+, 24, 15, and 23+ months, respectively. Peripheral hematologic response was achieved after three months for the four patients. All of them had normal monocyte count. The three complete responders had a rapid reduction of bone marrow hairy cell infiltration one month after the onset of CT and a delayed disappearance of reticulin fibrosis three months after beginning CT. Within three months, the bone marrow specimens from these three patients demonstrated rich and normal cellularity. Patient 3 had a complete response lasting 15 months. A bone marrow biopsy specimen obtained at the 15th month demonstrated one hairy cell focus located within the normal marrow cellularity. The patient received further therapy with chlorambucil. A bone marrow biopsy specimen obtained 28 months after the onset of induction CT did not show any residual disease. Bone marrow specimens from patient 6 showed the presence of residual hairy-cell microfoci and fibrosis persisting unchanged after 23 months.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>To Splenectomy (mo)</th>
<th>To Onset of Chemotherapy (mo)</th>
<th>Previous Treatment</th>
<th>Pulmonary Infection (g/dL)</th>
<th>Neutrophils (10^9/L)</th>
<th>Platelets (10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>2</td>
<td>4</td>
<td>Prednisone (2)</td>
<td>9.5</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>M</td>
<td>3</td>
<td>9</td>
<td>Prednisone (2)</td>
<td>7</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>F</td>
<td>4</td>
<td>36</td>
<td>Lithium carbonate (3)</td>
<td>8</td>
<td>0.05</td>
<td>120</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>0</td>
<td>7</td>
<td>Prednisone (1)</td>
<td>Two episodes of FUO* bilateral arthritis (viral ?)</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>M</td>
<td>12</td>
<td>72</td>
<td>Prednisone (3)</td>
<td>Three episodes of FUO* Severe cutaneous herpes</td>
<td>7.2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>M</td>
<td>32</td>
<td>34</td>
<td>Three episodes of FUO* bilateral arthritis</td>
<td>Furunculosis</td>
<td>12</td>
<td>0.3</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>M</td>
<td>6</td>
<td>18</td>
<td>Prednisone (3)</td>
<td>Two episodes of FUO* Pulmonary infection Anal abscess</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

* Fever of unknown origin.
Three patients (Nos. 4, 5, and 7) died during aplasia two months after the onset of therapy. Bone marrow biopsy specimens from patients 4 and 7 showed a complete clearing of leukemic infiltration by day 30 and 60, with profound hypocellularity. Biopsy specimens from patient 5 on days 40 and 60 showed the persistence of hairy cells and fibrosis in the bone marrow. A diffuse leukemic infiltration of the liver and lymph nodes was found at autopsy.

**Toxicity**

The toxicity of the induction regimen is summarized in Table 2. The mean duration of aplasia (neutrophil counts < 0.5 x 10⁹/L and platelet counts < 30 x 10⁹/L) for the four responding patients was 37 days (range, 32 to 45 days).

All seven treated patients experienced prolonged periods of fever (>38°C) during therapy and were treated with empiric antibiotherapy after blood cultures, stool cultures, and pharyngeal cultures. In two patients, bacteremia was diagnosed and *Staphylococcus albus* was isolated. The two patients recovered under specific antibiotherapy. Three viral mucocutaneous infections occurred. Patient 4 died on day 60 after beginning therapy of a refractory pneumonia caused by *Acinetobacter xylososyndens*. Biopsy showed a deseric and edematous bone marrow exempt of hairy cells. Patient 5 died on day 55 of a diffuse pulmonary and pericardial aspergillus infection while under therapy with 5-fluorocytosine and amphotericin B. Patient 7 died on day 60 of diffuse aspergillosis while under systemic antifungal therapy. After remission was attained, patients 1 and 2 received monthly maintenance therapy. Patient 2 died ten days after the 22nd course of maintenance therapy of possible septic shock in another hospital. Patient 1 received maintenance therapy for two years and has remained treatment free for 20 months.

### DISCUSSION

Seven hairy cell leukemia patients with severe bone marrow insufficiency were treated with intensive chemotherapy (CT). Four patients had a response; three achieved complete remission according to hematologic and histologic criteria similar to those for acute nonlymphoblastic leukemia (ANLL). The fourth patient achieved a partial response, with return of hematologic values to normal in the peripheral blood but with persistence of small foci of hairy cells in the bone marrow. Three patients died during aplasia, one of them with massive diffuse leukemic infiltration, the others with severe bone marrow hypoplasia. Finally, a patient with a complete response died on resumption of maintenance therapy 24 months after induction therapy. To date, three patients are alive and in excellent condition 23, 32, and 44 months after treatment.

So far, there have been very few reports of patients achieving complete remission according to bone marrow histologic criteria after chemotherapy. Reduction of bone marrow infiltration and improvement of platelet and red cell counts after a variety of cytotoxic agents such as low doses of chlorambucil have been reported. The report by Quesada et al on the use of alpha interferon seems very promising and needs to be quickly confirmed. It remains to be determined whether alpha interferon is effective in patients who fail to respond after splenectomy and who develop severe bone marrow insufficiency with anemia, severe granulocytopenia and severe recurrent infectious episodes.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Duration of Aplasia (d)</th>
<th>Documented Infection</th>
<th>Response to Therapy</th>
<th>Follow-up From Therapy (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>Cutaneous herpes hominis</td>
<td>CR</td>
<td>44 (A)</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>Septicemia: <em>Staphylococcus albus</em></td>
<td>CR</td>
<td>24 (D)</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Cutaneous herpes hominis</td>
<td>CR</td>
<td>32 (A)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Pneumonia: <em>Acinetobacter xylososyndens</em></td>
<td>No HC in BM Biopsy</td>
<td>- (D)</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>Pericarditis pneumonia: <em>Aspergillus</em></td>
<td>No R</td>
<td>- (D)</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>Septicemia: <em>Staphylococcus albus</em></td>
<td>PR</td>
<td>23 (A)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>Septicemia, meningitis: <em>Aspergillus</em></td>
<td>No HC in BM Biopsy</td>
<td>- (D)</td>
</tr>
</tbody>
</table>

A, alive; D, deceased; CR, complete response; PR, partial response; HC, hairy cells.
Reports of high-dose chemotherapy regimens are very scarce. Two young patients were submitted to high-dose zorubicine hydrochloride by Stewart et al.\textsuperscript{24} One of them had a complete hematologic response, and the bone marrow aspirate was free of hairy cells 15 months after therapy. The second patient, although having a good hematologic response, had persistence of leukemic cells. One patient was reported by Davis et al\textsuperscript{12} as achieving a prolonged complete response following an intensive regimen including cyclophosphamide and arabinosyl cytosine. MacCarthy and Catovsky\textsuperscript{25} treated a patient with doxorubicin and obtained great improvement of the peripheral hematologic values.

Finally, a recent report by Cheever et al\textsuperscript{26} described a complete response assessed on bone marrow histology after high-dose cyclophosphamide and total irradiation, followed by bone marrow graft from an identical twin. In this case, the authors describe, as we do here, a progressive clearance of fibrosis after therapy.

The regimen administered to our patients contains, like the above reports, an anthracycline, arabinosyl cytosine, and cyclophosphamide, which seem to be the most efficacious drugs in treating severe forms of this disease.

Some of the cases reported in the literature and four of the seven patients treated here had a prolonged remission according to bone marrow histologic criteria. In these patients, clearing of hairy cells was relatively quick, within one month, whereas disappearance of fibrosis was usually slow and delayed, up to three months. By this time, bone marrow cellularity was normal for all the patients. When a complete or partial response can be obtained, it seems that it will be prolonged, since our four patients had 23- to 44-month follow-up after therapy. Except for patient 2, who died of septic shock, none of these patients needed further red cell transfusions or treatment for infection. The long-term persistence of the response might be related to the slow development kinetics of the disease.\textsuperscript{29}

Whether a complete histologic response has been achieved needs further investigation. One of our patients with a partial response has not shown any progression of the disease after 23 months.

Toxicity in this group of patients was variable. Three patients died during initial therapy, and one patient with a complete response died, of maintenance regimen toxicity after 24 months. Duration of aplasia for the four patients who recovered from initial pancytopenia was much longer than what we\textsuperscript{30} observed with the same treatment given to relapsing ANLL patients (37 days for HCL v 25 days for ANLL). This could be explained by a slow disappearance of the cells involved, by a stem cell inhibitory factor synthetized by HCL,\textsuperscript{31} or by persistence of fibrosis. Indeed, the complete responding patients reported in the literature had aplasia lasting from 38 to 73 days\textsuperscript{31-33,24}

The prognostic factors and the therapeutic indications are not yet clearly defined and remain a major problem. A review of 211 patients with hairy cell leukemia followed in our department\textsuperscript{13} showed, as did Jansen\textsuperscript{4}, the detrimental effects on survival of thrombocopenia and neutropenia less than $0.5 \times 10^9/L$ at initial examination. We also found that a seriously impaired general condition (weight loss, marked asthenia, reduced performance status) and severe bleeding were the only initial clinical factors related to survival. Regarding splenectomized patients, we observed a tendency to different prognoses according to postsplenectomy neutropenia, which nonetheless failed to reach significance ($P = .09$). These results are in agreement with the data of Jansen\textsuperscript{12} and Catovsky\textsuperscript{1} based on similar categories of patients. During the last four years, five other patients who were previously splenectomized had "bad prognosis" characteristics and therefore met the chemotherapy treatment criteria. However, they were not treated because of refusal, personal reasons, or active infectious complications. All five patients died of severe infection three to 12 months after chemotherapy was indicated. The effectiveness of chemotherapy surely cannot be evaluated from our nonprospective and nonrandomized study. However, from our experience and from the experience of others, we know that complete and prolonged remissions can be obtained. Therefore, such combination chemotherapy should be used only for selected patients, ie, those who respond to splenectomy poorly as well as those patients with severe pancytopenia without splenomegaly. If the effectiveness of interferon therapy is confirmed, it could be the first choice for treatment. Intensive chemotherapy should be restricted to patients who fail to respond to interferon therapy. Further answers to this problem can only be provided by a prospective study.

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Intensive chemotherapy of hairy cell leukemia in patients with aggressive disease

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