The Effectiveness of Rubidzone in Hairy Cell Leukemia (Leukemic Reticuloendotheliosis)

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Two patients with hairy cell leukemia treated with the anthracycline antibiotic rubidzone are presented. One achieved a complete remission and the other a good partial hematologic and bone marrow remission. Neither has relapsed (at 20 and 13 mo, respectively), and neither has been retreated. Intensive supportive measures were required during the prolonged myelosuppression that followed treatment. The relative youth of the patients (ages 24 and 39 yr) may have contributed to their ability to survive until normal marrow recovered. Chemotherapy should not be employed in the initial management of hairy cell leukemia. However, if life-threatening granulocytopenia and thrombocytopenia occur secondary to bone marrow replacement by leukemic cells, and improvement does not occur using alternative methods of therapy, consideration could be given to chemotherapy with rubidzone. Facilities for intensive supportive care should be available.

Hairy cell leukemia (leukemic reticuloendotheliosis) is an uncommon condition with a very variable course. While some patients have survived 10–15 yr beyond diagnosis,1,2 others have died of sepsis or bleeding within a few days of presentation.2 Splenectomy is recognized as the initial treatment of choice1,3–11 and often results in an increase in circulating red cells, granulocytes, and platelets. However, improvement is sustained in only one-third of all cases.11 Hematologic parameters often deteriorate after months to years, and death is usually the result of infection.1,7,14–13 Although some authors have noted improvement following corticosteroids,14 androgens,13,14 or chemotherapy,11,13,15–20 the response to cytotoxic agents is considered suboptimal. Generally, chemotherapy should be employed in patients with hairy cell leukemia only if a life-threatening situation develops because of severe neutropenia or thrombocytopenia secondary to bone marrow replacement by leukemic cells. In this article, we report the encouraging results obtained in treating two such patients with the anthracycline antibiotic, rubidzone. Informed consent was obtained from both patients after the investigational nature of the treatment had been fully explained. These are the only patients with hairy cell leukemia that we have treated with rubidzone.

CASE REPORTS

Case 1

A 39-yr-old man was referred to M. D. Anderson Hospital in October 1976 with a diagnosis of leukemia. He had a 3-wk history of easy bruisability, increasing fatigability, low-grade fever, and the
recent onset of pancytopenia. Physical examination revealed multiple ecchymoses of the skin. The spleen was enlarged, firm, and palpable 6 cm below the left costal margin. There was no lymphadenopathy or hepatomegaly. His hemoglobin (Hb) was 10.8 g/dl, platelet count 49,000/μl, and WBC 2600/μl with 18% neutrophils, 78% lymphocytes, and 3% monocytes. Bone marrow aspiration showed 0.2% blasts, 28% lymphocytes, and 14% cells suggestive of hairy cell leukemia. Bone marrow biopsy suggested the diagnosis of hairy cell leukemia. Cytogenic studies were normal. Because of pancytopenia, a splenectomy was performed 2 wk after presentation. Hairy cells were found to be infiltrating spleen, splenic lymph nodes, and liver in a pattern typical of hairy cell leukemia. Postoperatively, the WBC rose to 3100/μl with 87% neutrophils, 10% lymphocytes, and 2% monocytes, and the platelet count rose to 137,000/μl. He had a gradual increase of leukemic infiltrate in the bone marrow and presented 5 mo later (March 1977) with anemia, ecchymoses, and epistaxis. His Hb was 8.3 g/dl, his platelet count was 20,000/μl, and his WBC was 8900/μl with 73% lymphocytes and 27% hairy cells. Bone marrow aspiration showed 74% hairy cells and a cellularity of 95%.

Because of the severity of the granulocytopenia and thrombocytopenia, treatment was started with rubidazone at 450 mg/sq m. By day 4, no hairy cells were detectable in the peripheral smear, but on day 13, a bone marrow biopsy showed 100% cellularity with 100% leukemic cells. Rubidazone (450 mg/sq m) was repeated on day 17 of the first course. At that time, his platelet count was 16,000/μl, and his WBC was 1800/μl with 95% lymphocytes, 3% neutrophils, and 2% monocytes. Platelet count and WBC remained depressed. On day 13 of course 2, a bone marrow biopsy revealed a hypocellular marrow with no evidence of leukemic cells. The patient remained myelosuppressed. Fifty days after the second dose of rubidazone, the bone marrow cellularity on biopsy was still less than 5%. His platelet count was 32,000/μl, and his WBC 600/μl with 22% neutrophils, 74% lymphocytes, and 4% monocytes. Lithium carbonate (300 mg p.o. q.i.d.) was initiated in an attempt to stimulate marrow recovery. Six days later the patient was discharged from the hospital with a platelet count of 57,000/cu mm and a WBC of 1000/sq mm with 26% neutrophils. He returned 75 days after his second dose of rubidazone with a platelet count of 284,000/μl and a WBC of 2600/μl with 69% neutrophils and 1% monocytes. Bone marrow at that time showed a 10% cellularity with no evidence of hairy cells. At last follow-up visit, 15 mo following initiation of treatment, the patient felt and looked well. His Hb was 16.1 g/dl, platelet count was 350,000/μl, and WBC was 6600/μl with 43% neutrophils, 40% lymphocytes, 16% monocytes, and 1% basophils. Bone marrow aspiration was interpreted as normal, with 35% cellularity. Lymphocyte surface marker analysis was normal with 83% T cells, 11% B cells, 1% C3-receptor-positive cells, and 14% FC-receptor-positive cells. Blood counts done by the referring physician 20 mo following treatment disclosed an Hb of 16.4 g/dl, a platelet count of 318,000/μl, and a WBC of 7800/μl with 93% neutrophils, 5% lymphocytes, 2% monocytes, and 2% eosinophils. Treatment has not been repeated.

Following treatment, intensive supportive therapy was needed with prophylactic platelet transfusions, therapeutic granulocyte transfusions, red blood cell transfusions, and antibiotics. He had numerous febrile episodes, with one episode of pneumonia (no organism recovered). Twelve days after the first dose of rubidazone, a firm erythematous maculonodular lesion was noted on the medial aspect of the right knee. Biopsy revealed Allescheria boydii. The lesion became deeply ulcerated, then gradually healed on treatment with systemic amphotericin B and granulocyte transfusions.

**Case 2**

A 24-yr-old male was referred to M. D. Anderson Hospital in June 1977 with a diagnosis of leukemia. He had a 4-day history of vomiting, abdominal pain, fever, and diaphoresis. Past history was remarkable in that he had received pharyngeal irradiation as a child for recurrent tonsillitis. On examination he was noted to have massive splenomegaly with tenderness and a friction rub over the spleen. A few shotty lymph nodes were palpable in each axilla. Numerous small pustules were present over the upper trunk. Culture of these grew staphylococcus epidermidis. His Hb was 13.3 g/dl, his platelet count was 49,000/μl, and his WBC was 43,000/μl with 3% neutrophils, 6% lymphocytes, and 91% leukemic cells. Bone marrow aspiration revealed 62% leukemic cells consistent with hairy cell leukemia, and the tartrate-resistant acid phosphatase was positive. Bone marrow cellularity was 35% on clot section, but 70% on bone marrow biopsy. Lymphocyte surface marker analysis revealed 11% T cells, 89% B cells, 10% C3-receptor-positive cells, and no FC-receptor-positive cells. Cytogenetic studies were normal.

The patient's abdominal pain and fever resolved with no treatment. Because of the thrombocytopenia and granulocytopenia, the patient underwent a splenectomy 2 wk after presentation. Hairy cells were found to be infiltrating spleen, splenic lymph nodes, and liver. One week postoperatively, his platelet
count was 420,000/µl, and his WBC was 22,800/µl with 14% neutrophils, 51% lymphocytes, 1% monocytes, and 34% hairy cells. The patient then did well until 5 mo postoperatively, at which time he returned asymptomatic but with a WBC of 66,500/µl with no neutrophils and no monocytes. His platelet count was 130,000/µl, and his Hb was 14.8 g/dl. Bone marrow aspiration showed 71% leukemic cells with a 70% cellularity. Erythroid and granulocytic precursors and megakaryocytes appeared to be normal. Because of the severe granulocytopenia, treatment was initiated with rubidazone at 450 mg/sq m. Twelve days after treatment, the WBC had decreased to 27,000/µl with 88% leukemic cells and 12% lymphocytes, and the platelet count had decreased to 59,000/µl. Nineteen days after treatment, the WBC was 900/µl with 64% neutrophils, 35% lymphocytes, and 1% hairy cells, and the platelet count had recovered to 138,000/µl. By 36 days after treatment, the WBC had risen to 2000/µl with 55% neutrophils, 45% lymphocytes, and no hairy cells; by day 46, the Hb was 10 g/dl, the platelet count was 510,000/µl, and the WBC was 6300/µl with 71% neutrophils, 27% lymphocytes, and 2% monocytes. Bone marrow aspirates on days 31, 36, 37, and 45 after treatment showed, respectively, 40%, 2.5%, 40%, and 8% hairy cells, implying residual patchy involvement of the marrow. Bone marrow biopsies on those days were interpreted as being free of hairy cells. His last follow-up was 13 mo after initiation of treatment at which time he looked and felt well, with a Hb of 16.1 g/dl, platelet count 361,000/µl, and WBC of 7800/µl with 76% neutrophils and 24% lymphocytes. Bone marrow aspiration at that time showed 24% hairy cells and 40% cellularity. Bone marrow biopsy confirmed that infiltration of the marrow by hairy cells was patchy. Lymphocyte surface marker analysis performed 5 mo after treatment was normal with 75% T cells, 19% B cells, 8% FC-receptor-positive cells, and 11% C3-receptor-positive cells. No further treatment has been given.

As with the first patient, intensive supportive therapy was needed because of prolonged myelosuppression during remission induction, with platelet transfusions, WBC transfusions, and antibiotics. Two weeks after initiation of treatment, he was readmitted with Staphylococcus aureus septicemia and pneumonia. Cultures became negative on antibiotics, but the patient remained febrile with a pneumonic infiltrate in both lungs. Eleven days after admission, an open-lung biopsy was performed that showed interstitial fibrosis. Cultures were initially negative. Antibiotics were discontinued and prednisone therapy initiated. The patient rapidly defervesced and experienced improvement of pulmonary function. Nine days later, the patient spiked a temperature and was noted to have cavitation on his chest x-ray. Propionibacterium acnes was noted to be growing in lung biopsy specimens from 2 wk earlier. Carbenacillin and clindamycin were then administered for 2 wk, and prednisone was continued. The patient was discharged feeling well with residual scarring on his chest x-ray but normal pulmonary function, and prednisone was gradually tapered without incident.

DISCUSSION

These are the first cases of hairy cell leukemia that we are aware of treated by the anthracycline antibiotic, rubidazone. They illustrate that rubidazone appears to be highly effective in this disease. Both patients had initially benefited from splenectomy, then showed unequivocal evidence of progressive leukemic infiltration of the bone marrow with failure of production of normal hematologic elements. In both, gradual clearing of leukemic elements from bone marrow and/or blood occurred following high-dose therapy with rubidazone, and both experienced prolonged myelosuppression requiring intensive supportive therapy during recovery. One achieved a partial remission persisting now for 13 mo. The other achieved a complete remission. The most recent bone marrow aspiration and biopsy, performed 15 mo after initiation of chemotherapy, showed no evidence of recurrence. Blood counts at 20 mo after chemotherapy were completely normal. Further treatment has not been necessary in either patient.

Chemotherapy has been of little benefit in hairy cell leukemia. In the past, patients at our institution have received a variety of agents alone or in combination, including adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin, arabinosyl cytosine, cis-diammine dichloroplatinum, and androgens. Therapeutic
benefit has been minimal or nonexistent. Experience with anthracyclines other than rubidazone is limited. One patient is reported to have derived no benefit from adriamycin, whereas another had myelosuppression followed by hematologic improvement when treated with daunorubicin, arabinosyl cytosine, and prednisone. Although rubidazone has not been used in hairy cell leukemia in the past, it has been our experience that it is the most active agent yet tested in acute myelogenous leukemia and is also highly active in acute lymphoblastic leukemia. It produces a rapid decrease in circulating leukemia cells followed by rapid recovery of normal hematologic elements, and death during remission induction is significantly less frequent than with daunorubicin. From the cases reported here, it appears that this high antileukemic activity also extends to hairy cell leukemia. It should be stressed however, that the success in the two patients we have presented was at least partially due to our ability to support them through periods of prolonged myelosuppression. In addition, both patients were considerably younger than most patients with hairy cell leukemia, and this undoubtedly contributed to their recovery.

A handful of patients with hairy cell leukemia do appear to have responded well to other forms of treatment. Davis reported a patient who went into complete remission with a combination of cyclophosphamide and arabinosyl cytosine after having shown no response to vincristine and prednisone. Their patient, like ours, required intensive supportive measures during remission induction and was myelosuppressed for 38 days. The patient is still in remission 20 mo after treatment. Schnitzer reported one case treated with vincristine and prednisone who had a normal bone marrow biopsy 10 mo later. However, the patient's leukopenia had not resolved, and the biopsy was not repeated a second time to rule out patchy involvement. A transient complete remission has also been noted with cyclophosphamide, vincristine, and prednisone. A patient treated with arabinosyl cytosine, vincristine, and prednisone had a decrease of hairy cells in the bone marrow from 85% to 35%, with a concomitant decrease in spleen size and circulating hairy cells. A combination of etiocholanolone plus prednisone has resulted in resolution of anemia, granulocytopenia, and thrombocytopenia after several weeks of treatment, and normalization of the peripheral smear and hematologic parameters has been noted after prolonged treatment with the androgen, oxymethalone, although the leukemic infiltrate in the bone marrow did not change.

On the other hand, results have been disappointing with other agents, and at best, only transient hematologic improvement has been seen with vinca alkaloids, alkylating agents such as cyclophosphamide, chlorambucil, T.E.M., and nitrogen mustard, androgens other than etiocholanolone and oxymethalone, 6-mercaptopurine plus procarbazine, radioactive phosphorus, and splenic irradiation. Moreover, it has been noted that survival decreases and risk of serious infection rises dramatically following treatment with alkylating agents in association with the prolonged myelosuppression that frequently occurs, and risk of life-threatening infection also rises markedly with prednisone use. It is difficult to determine from the literature the comparability of groups receiving chemotherapy; it is possible that primarily poor prognosis patients are selected for treatment.
The difficulty in achieving chemotherapeutically induced remissions appears to be due to two major factors. First, hairy cells appear to be very slow growing and hence less susceptible to chemotherapy. This is suggested by the prolonged survival of some patients, the low rate of increase of leukemic infiltrate in the bone marrow, and the small number of cells in mitosis. The second major problem relates to the defective bone marrow reserve in hairy cell patients. Prolonged periods of myelosuppression have been noted following cytoreductive chemotherapy even if substantial killing of hairy cells occurs. Increased reticulin fibers are well described in the marrow of hairy cell leukemia patients, and some authors have also noted increased collagen deposition. These fibers might possibly interfere with production of normal hematologic elements.

Moreover, although the cell of origin of hairy cell leukemia has been variously postulated to be the B lymphocyte, a subpopulation of B lymphocytes that possess phagocytic properties, the monocyte, or the T lymphocyte, there is suggestive evidence that a basic stem cell disorder exists. Abnormalities have been noted in platelet, granulocyte, and erythrocyte morphology. Unlike the normochromic normocytic erythrocytes found in myelophthisic anemia and myelofibrosis, a number of authors have noted macrocytosis in their hairy cell leukemia patients, and 13 of our 18 patients had macrocytosis. In addition, decreased numbers of T lymphocytes have been noted along with an abnormal response to phytohemagglutinin (PHA), and a defect in cell-mediated immunity has been suggested in view of the high incidence of atypical mycobacterial infections. Monocyte dysfunction has also been noted. This broad spectrum of abnormalities involving many cell lines suggests the possibility that a stem cell disorder exists in hairy cell leukemia. It may either represent the basic defect in the disease or may instead be the result of damage to stem cells by the same hypothetical agent that caused the emergence of the leukemic population from another cell line. In either case, a defect in stem cells could partially explain the prolonged recovery time required following chemotherapy in this disease.

In conclusion, rubidazone is an effective chemotherapeutic agent in hairy cell leukemia. Splenectomy remains the initial treatment of choice, since many patients benefit at least transiently; but once severe granulocytopenia and thrombocytopenia occur and chemotherapy becomes necessary, rubidazone is a logical agent to use. We have demonstrated both its effectiveness in eradicating leukemic cells and the recovery of normal hematologic elements following its use. It must be stressed, however, that facilities for intensive supporting care must be available during remission induction.

REFERENCES

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