Response to 2'-Deoxycoformycin After Failure of Interferon-α in Nonsplenectomized Patients With Hairy Cell Leukemia

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Two patients with hairy cell leukemia with massive splenomegaly and severe pancytopenia were treated with recombinant α-A interferon (IFN-α-2a). There was no significant response to a trial of IFN-α-2a (11 and 20 weeks) with respect to blood counts or spleen size. Subsequent treatment with 2'-deoxycoformycin (dCF) for 8 consecutive weeks (4 mg/m²/wk) resulted in normalization of spleen size and a normalization of peripheral blood counts and bone marrow in one patient. The second patient demonstrated a reduction in spleen size and improved blood counts following 9 weeks of dCF therapy but eventually became refractory. This demonstrates that dCF is non-cross-resistant with interferon and confirms the efficacy of dCF in nonsplenectomized patients.

Hairy cell leukemia is a lymphoproliferative disorder generally involving B lymphocytes and usually presents with cytopenias and splenomegaly.12 Standard initial therapy has been splenectomy, which often restores hematologic parameters to normal.3-5 Unfortunately, most of these patients relapse with recurrent cytopenias weeks to years following splenectomy. Treatment with cytotoxic agents such as chlorambucil may result in a temporary improvement in hematologic parameters.6 However, these patients relapse with recurrent cytopenias weeks to years following splenectomy. We and others have reported similar responses to recombinant interferon-α, with greater peripheral blood counts.7-10 Since most patients receiving interferon-α to date have had prior splenectomy, the clinical efficacy of interferon-α in nonsplenectomized patients remains uncertain.

Even more recently, the lymphocytotoxic agent, 2'-deoxycoformycin (dCF), or pentostatin, was reported to have induced rapid, complete remissions in patients with hairy cell leukemia.11 dCF is a tight-binding inhibitor of adenosine deaminase (ADA). The enzyme responsible for the conversion of adenosine to inosine and deoxyadenosine to deoxyinosine. In the absence of ADA activity, deoxyadenosine is phosphorylated to deoxyadenosine triphosphate (dATP) rather than deaminated to deoxyinosine, which may contribute to the lymphocytotoxicity.12 The biochemical basis for this toxicity remains controversial, and recent studies have suggested that the principal cause of cell death in normal resting human lymphocytes is depletion of NAD.13 The drug has been used successfully in the treatment of acute lymphoblastic leukemia, but has been associated with severe toxicity when used in higher doses.14 Clinical nonlymphoid toxicity has been correlated with depletion of ATP15 and with accumulation of dATP in red cells.16,17 Further confirmation of the promising results with dCF in patients with hairy cell leukemia as well as the apparent lack of toxicity is needed, and the comparative efficacy of interferon-α vs dCF in this disease remains to be demonstrated. We report the results of dCF therapy in two nonsplenectomized hairy cell leukemia patients who had failed prior therapy with recombinant α-A interferon (IFN-α-2a).

MATERIALS AND METHODS

Patient 1. The first patient was a 42-year-old Romanian male who was in apparent good health until March 1984 when he noted the insidious onset of fatigue, weight loss, and exertional dyspnea. These symptoms progressed, and in Aug 1984, he was admitted to the University of Michigan Medical Center with acute epistaxis. Physical examination was significant for moderate epistaxis without an obvious source. The liver was enlarged with a 24-cm span, and the spleen was palpable 12 cm below the left costal margin. The remainder of his examination was unremarkable.

Initial laboratory data included a hemoglobin level of 4.9 g/100 mL, hematocrit value of 15.7%, and a platelet count of 41 x 10⁹/L. The white blood count was 4.3 x 10⁹/L with 14% neutrophils, 3% bands, 81% lymphocytes, 2% monocytes, plus 13 nucleated red cells. Most of the lymphoid mononuclear cells were noted to have bean-shaped nuclei and ragged cytoplasmic margins typical of hairy cells. Tartrate-resistant acid phosphatase stain was positive, and bone marrow biopsy results confirmed the diagnosis of hairy cell leukemia.

The epistaxis was controlled with local packing and transfusion of random donor platelets and packed red cells. Splenectomy was strongly recommended but was refused by the patient.

For the next month, the patient was treated supportively with platelets and packed red cells for recurrent epistaxis as well as with multiple antibiotics for episodes of fever. He continued to refuse splenectomy on repeated occasions.

In Sept 1984, the patient was referred to the Biological Response Modifiers Program of the National Cancer Institute. Following the patient’s informed consent, he underwent a 12-week trial of IFN-α-2a (Hoffmann-La Roche Inc, Nutley, NJ) administered on a daily basis subcutaneously at a dose of 3 x 10⁶ U/d from Sept 24 through Dec 11, 1984. Although during this period his epistaxis subsided and his transfusion requirements appeared to decrease somewhat, his severe pancytopenia and massive hepatosplenomegaly persisted. Due to a failing platelet count with recurrent petechiae and epistaxis, the interferon therapy was discontinued.

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Six weeks after stopping IFN-α-2a therapy and following the patient's informed consent, he began to receive dCF at a dose of 4 mg/m²/wk as an intravenous (IV) bolus followed by a liter of normal saline infused for a period of one to two hours. Allopurinol, 300 mg/d orally, was also given during the first week.

Patient 2. The second patient was a 65-year-old Pakistani woman who had had a 15-year history of splenomegaly ultimately diagnosed as hairy cell leukemia in 1979. She was treated with a number of courses of cytotoxic chemotherapy (chlorambucil and cyclophosphamide) but was not considered a good surgical candidate. She was referred to the National Cancer Institute for IFN-α-2a therapy. Physical examination was significant for a massively enlarged spleen (approximately 30 cm below the left costal margin). Her liver was palpable 9 cm below her right costal margin.

Initial laboratory data revealed a hemoglobin level of 11.5 g/100 mL, hematocrit value of 35%, and platelet count of 92 × 10^9/L. The WBC count was 133 × 10^9/L with 2% neutrophils, 0% bands, 0% monocytes, and 98% lymphocytes having the characteristic appearance of hairy cell leukemia cells. Tartrate-resistant acid phosphatase stain was positive, and bone marrow biopsy results confirmed the diagnosis of hairy cell leukemia.

On Dec 17, 1984, the patient began a daily dose of 3 × 10^6 units of rIFN-αA (informed consent was obtained prior to therapy). There were no changes in any of the laboratory or physical parameters throughout the course of 20 weeks of therapy. She was subsequently treated with dCF at a dose of 4 mg/m²/wk as previously described (informed consent was obtained prior to therapy). Allopurinol therapy, 300 mg/m² orally, was also begun.

Measurement of intracellular adenine nucleotides. Red cell ATP and dATP were measured using previously reported techniques.46

Criteria for response. Complete remission was defined as the absence of hairy cells in the bone marrow aspirate and biopsy specimen, bone marrow granulocytes above 35%, and recovery of the hemoglobin level to ≥12 g/dL, the absolute granulocyte counts to ≥1.5 × 10^9/L, and the platelet counts to ≥100 × 10^9/L for ≥1 month. Partial remission was defined as a decrease of the hairy cell leukemia infiltrate by more than 50% from pretreatment levels and bone marrow granulocytes above 35%, with recovery of peripheral blood parameters as defined for complete remission for ≥1 month. Minor remission was defined as a decrease of the hairy cell leukemia infiltrate by <50% from pretreatment values, bone marrow granulocytes of 25% to 35%, and improvement of peripheral blood parameters for ≥1 month. Stabilization was defined as stabilization of all detectable abnormalities of bone marrow, peripheral blood, and physical examination. Progression was defined as the appearance of new, or worsening of preexistent abnormalities of peripheral blood, bone marrow, or physical examination. The duration of response was measured in terms of the number of days from the initial documentation of response to the documentation of progression.

RESULTS

No subjective or objective toxicity was observed during treatment with dCF in the first patient. Within 1 week after receiving his first dose of dCF, improvement was seen, with a decrease in liver and spleen size and reduction in circulating hairy cells. The platelet count and hepatosplenomegaly continued to improve progressively, and both parameters were within normal limits by week 8 of treatment (Fig 1). Also, by the eighth week of treatment, the absolute granulocyte count rose to 1 × 10^9/L (gradually rose to 2.6 × 10^9/L), and there were no longer visible hairy cells or nucleated erythrocytes on the peripheral blood film. Although he had no toxicity, the patient refused further therapy after week 8 because he was feeling well. Despite no further therapy, the patient’s hematocrit value continued to improve and by week 16 was 41%. A bone marrow biopsy specimen showed normal hematopoietic cells without hairy cells. Red cell ATP remained within normal limits (135 to 156 [picomoles] pmol/10^6 cells), and red cell dATP rose no higher than 8.9 pmol/10^6 cells during treatment with dCF (data not shown).

The patient was lost to follow-up, but 7 months later agreed to return for an examination and blood count; he refused a bone marrow aspiration and biopsy. His hemoglobin level was 15 g/dL; hematocrit value, 45%; platelets, 114 × 10^9/L; and WBC count, 3.6 × 10^9/L (60% neutrophils, 10% bands, 29% lymphocytes, 1% monocytes). The peripheral blood smear revealed no hairy cell leukemia cells, but some very large abnormal appearing platelets were noted. His spleen was not palpable, and he had no physical complaints.

Patient 2 did not have a dramatic response to weekly injections of dCF but did have a rapid reduction in the circulating hairy cells from 179 × 10^9/L to 23 × 10^9/L during her ninth week of therapy, with improvement in her hematocrit value from 28% to 36% and stable platelet counts. Her spleen decreased in size from 30 cm to 16 cm below the left costal margin. A skin rash and keratoconjunctivitis developed in week 6, leading to a reduction of therapy to 4 mg/m² every other week for the next 12 weeks. Following this therapy, her white count increased, and she was given 4 mg/m² of dCF on two successive days. Her WBC count continued to rise despite stable hematocrit and platelet counts, and she was switched to chlorambucil treatment. She

![Fig 1. Clinical and laboratory parameters in patient 1 during and following interferon and dCF therapy. Arrows represent RBC transfusions. LCM, left costal margin.](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAABZAAAABgCAYAAACsHw1gAAAABGdBTUEAALG+IgAABJElEQ过后 was referring to October 15, 2017, for personal use only.)
did not respond to chlorambucil therapy and eventually was taken to surgery for a splenectomy. She had a transient minor response to splenectomy.

**DISCUSSION**

Within the past 2 years, two new therapeutic agents have shown exceptional promise for the treatment of hairy cell leukemia. Both interferon-α and dCF have been reported to induce complete remissions in this disease, with early results appearing far superior to conventional chemotherapeutic agents such as chlorambucil. Treatment-related toxicity has also been minor. Given the small numbers of patients reported, however, with only short-term observation, the relative efficacy of each of these agents remains uncertain with respect to extent of disease and prior therapy.

Neither of our patients had prior splenectomy. They received IFN-α-2a (11 and 20 consecutive weeks, respectively) but had no clear response to this therapy. Although these two patients may have eventually responded to interferon at the same dose or at increased doses, it was decided to discontinue the treatment because of progressive thrombocytopenia with fresh bleeding and petechiae in one patient and painful splenic infarcts in the other. Both patients were subsequently treated with dCF, a second investigational drug. After only eight weekly injections of dCF the first patient had a dramatic response, with normalization of peripheral counts and bone marrow and resolution of severe hepatosplenomegaly. Seven months later he had no hepatosplenomegaly and a normal hematocrit value. However, he had moderate leukopenia and thrombocytopenia suggestive of recurrent hairy cell leukemia in his bone marrow. Unfortunately, he refused a bone marrow aspiration and biopsy. The other patient had a transient improvement in blood counts and reduction in the size of her spleen. Preliminary data from Spiers and co-workers have confirmed the effectiveness of dCF in nonsplenectomized patients with hairy cell leukemia as well as its effectiveness after failure of interferon-α-18.

The failure of these two patients to respond to IFN-α-2a, contrary to the extremely high response rates in most patients, cannot be accounted for with certainty. Given the low efficacy of other forms of adoptive or active immunotherapy in the presence of high tumor burdens in laboratory animal models, it is possible that these patients might have responded if they had undergone prior splenectomy or if treatment had been started earlier in the course of the disease. Suboptimal drug delivery to tumor sites or an intrinsic resistance of the patient’s hairy cells to IFN-α-2a is also possible.

The optimum dose and frequency of dCF administration remains to be established. In phase I studies in acute leukemia, daily IV administration of dCF for three to seven consecutive days in doses of 0.15 to 1.0 mg/kg/d resulted in a fairly high incidence of gastrointestinal toxicity (nausea, vomiting, and diarrhea), with occasional keratoconjunctivitis, nephrotoxicity, hematotoxicity, CNS toxicity, or death.18 The two hairy cell leukemia patients with complete responses to dCF reported by Spiers et al11 initially received two or three consecutive daily IV boluses of dCF at a dose of 5 mg/m2 followed by two consecutive days of treatment every 2 weeks for a total of 15 or 16 doses. Reported toxicity to lower doses of dCF was moderately severe nausea and vomiting in one patient and a transient photosensitivity rash in both patients. Our patients were treated with a lower weekly dose of 4 mg/m2 without a loading dose. Despite the massive tumor burden, the rapidity of antitumor effect was nonetheless striking, and there was no demonstrable toxicity in one patient. The minimal increase in red cell dATP and decrease in ATP seen in this patient was consistent with the observed lack of toxicity.17 The second patient did not have a dramatic response to dCF, and her therapy was complicated by rash and keratoconjunctivitis. Unfortunately, we did not measure red cell adenine nucleotides in this patient. The treatment schedule chosen for our patients as induction therapy thus appears to be a reasonable one with respect to safety and efficacy, although the long-term toxicity of dCF in hairy cell leukemia patients remains to be studied. Toxicity in patient 2 was improved when therapy was decreased to every other week.

In summary, we report one complete response and one minor response to dCF in two nonsplenectomized hairy cell leukemia patients following their failure to respond to IFN-α-2a. Weekly outpatient low-dose dCF therapy without a loading schedule was extremely well tolerated. These cases confirm the responsiveness of hairy cell leukemia to dCF in nonsplenectomized patients with high tumor burdens and suggest a possible superiority of dCF over interferon-α in this setting as well as a lack of cross-resistance with interferon. Unanswered questions still remaining include remission duration and survival in responders to interferon-α and dCF and the role of maintenance therapy using either interferon-α or dCF. Although the dramatic resolution of splenomegaly in patient 1 with dCF raises the question of whether splenectomy should continue as first-line therapy for hairy cell leukemia, further study of the safety and efficacy of dCF with longer follow-up will be necessary before dCF can be recommended as first-line therapy outside of the investigational setting.

**REFERENCES**


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