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Long-Term Follow-Up of Patients With Hairy Cell Leukemia After Treatment With 2'-Deoxycoformycin

By Eric H. Kraut, Michael R. Grever, and Bertha A. Bouroncle

Twenty-four patients with advanced hairy cell leukemia treated with 2'-deoxycoformycin (dCF) were studied after achieving complete remission to determine the impact of treatment on survival, disease-free survival, long-term complications of treatment, and response to retreatment. At a median follow-up time of 82 months (range, 54 to 104 months), 23 of 24 patients remain alive. One patient has died of recurrent disease refractory to treatment. Of the remaining 23 patients, 11 have relapsed at a median time of 30 months (range, 7 to 80 months) after treatment completion. Of these 11 patients, 7 have been retreated with dCF or 2'-chlorodeoxyadenosine (2-CdA), including one patient that was retreated twice. All seven patients have responded,

MANAGEMENT of patients with hairy cell leukemia has dramatically changed with the introduction of three new agents: α interferon, 2'-deoxycoformycin (dCF; Nipent, Parke-Davis, Morris Plains, NJ), and 2'-Chlorodeoxyadenosine (2-CdA; Leustatin, Ortho Biotech, Raritan, NJ).¹⁻⁶ All three drugs can induce significant objective responses in hairy cell leukemia patients, although only dCF and 2-CdA have been shown to induce a high percentage of complete and lasting remissions.^{1,2,6,7} The impact that these treatments have had on short-term survival and morbidity has already been reported, but the long-term effect of treatment is still to be determined. We report a median 82-month follow up of 24 patients with hairy cell leukemia successfully treated with dCF and establish the long-term benefits of this therapy. The duration of remission, length of survival, long-term complications, and response to retreatment after relapse are reported for these patients.

MATERIALS AND METHODS

Patients. We evaluated 27 patients with hairy cell leukemia who had entered complete remission (CR) on our phase II protocol, after treatment with dCF (pentostatin). After achieving complete remission, the patients were observed without further treatment unless indicated.^{2,8} Patients entered into the treatment protocol met the following criteria: (1) a confirmed diagnosis of hairy cell leukemia on the basis of peripheral blood and bone marrow biopsy; (2) progressive disease, as demonstrated by anemia (hemoglobin level less than 12 g/dL), thrombocytopenia (platelet count less than 100,000/ μ L), neutropenia (neutrophil count less than 1,500/ μ L), and/or rising white blood cell (WBC) count with increasing number of hairy cells in the peripheral blood; and (3) normal hepatic and renal function with creatinine clearance rate greater than 60 mL/min. Two patients with creatinine clearance rates between 50 and 60 mL/min were treated after permission was obtained from the National Cancer Institute (NCI). Informed consent approved by The Ohio State University Human Subjects Review Board was obtained before administration of the drug.

Treatment protocol. The drug dCF was obtained from the Investigational Drug Branch of the NCI (Bethesda, MD). Patients received dCF at a dose of 4 mg/m² by intravenous (IV) bolus injection every other week. One patient with reduced renal function received 2 mg/m², and another patient with borderline normal renal function received 3 mg/m². A third patient received 2 mg/m² due to adverse effects of the drug at a higher dose.^{2,8} Patients were carefully moni-

with five patients achieving second complete remission. Two patients have had normalization of blood cell counts, but repeat bone marrows have not been performed. No serious infections have been seen in dCF-treated patients during follow-up. One case of Hodgkin's disease and three cases of skin malignancies have developed in these 24 patients. From initiation of treatment, survival is 93 months (range, 63 to 116 months). We concluded that dCF significantly prolongs the survival of patients with advanced hairy cell leukemia without resultant long-term complications. It is too early to predict if this therapy will be curative for the patients still in remission.

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tored for a change in clinical status by physical examination and peripheral blood count with a cell differential before each treatment. Treatment was modified in the case of a significant change in renal function or neutropenia according to the guidelines previously described.²

Response criteria. Patients in CR had an absence of hairy cells in the bone marrow aspirate and biopsy with restoration of the peripheral blood counts to the following values: hemoglobin level greater than 12 g/dL, platelet count greater than 100,000/ μ L, and neutrophil count greater than 1,500/ μ L. Patients with an enlarged spleen at initiation of therapy were required to have a normal size spleen by physical exam. Partial remission (PR) was defined as the absence of hairy cells in the peripheral blood and a 50% or greater reduction in the percentage of hairy cell infiltration in the bone marrow biopsy, improvement in peripheral counts as noted for CR, and 50% reduction of spleen size on physical exam. Minor response (MR) was defined as improvement in one or more of the peripheral blood elements as defined above, or a greater than 50% reduction in circulating hairy cells.

Follow-up. Patients were observed off treatment with physical examinations and complete blood counts every 3 to 6 months. Repeat bone marrow biopsies were performed in most patients at intervals of 6 months to 1 year or until relapse for the first 4 years. In some patients, routine bone marrows were not obtained due to transfer of care to their local physicians. After 4 years of follow up, we did not require bone marrows unless necessary for disease management. As not all patients had serial marrows, we cannot present an accurate duration of remission based on bone marrow observations; however, duration of survival and time to retreatment are presented.

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RESULTS

Of the 27 patients who originally went into CR after dCF treatment, 24 patients are available for long-term follow-up. Two patients moved, and no information on their clinical status could be obtained. One patient died of complications of pulmonary disease while in remission from hairy cell leukemia.

Of the 24 patients, 23 are alive at a median time of 84 months (range, 54 to 104 months) from the date of achieving CR. One patient died of refractory hairy cell leukemia, after treatment with dCF, 2-CdA, and fludarabine phosphate, 80 months after finishing initial treatment.

Of the remaining 23 patients, 11 had documented relapse at a median of 30 months (range, 7 to 80 months) from the end of treatment. Initial relapse in most patients was documented by bone marrow alone, often with minimal disease found (less than 5% hairy cell infiltration). These relapses did not always portend progressive disease, and several patients had normal repeat marrows. Patients were observed until falling blood cell counts and progressive bone marrow infiltration with hairy cells developed. Patients were then evaluated for retreatment, but no specific blood cell count was used to determine initiation of therapy. In addition, the choice of therapy was left to the treating physician.

Seven patients have been retreated at a median of 60 months (range, 13 to 86 months) from initial remission. Six of the seven patients were treated for granulocytopenia and/or anemia, and one patient was treated for bone marrow progression. Four of these seven patients received dCF treatment at relapse, with CR being obtained at initial retreatment in three patients. One of these three patients again relapsed after a second CR and has had a good partial response to dCF, with less than 5% hairy cells remaining in the marrow. One patient is still on treatment and has had normalization of his cell counts. The duration of second CRs after dCF were 8 months and 25 months in two of the patients. The third patient is still in remission after 2 months.

Three patients were retreated with 2-CdA after initial relapse. Two patients have obtained a CR and are being observed off-therapy for 8 and 14 months, respectively. One patient has had normalization of his cell counts, but repeat bone marrow biopsy has not been performed. The only significant complication seen in one of these seven patients at retreatment was a case of legionella pneumonia after 2-CdA.

There have been no serious infectious complications in any of the patients who were observed after discontinuation of dCF treatment. One patient developed herpes zoster 52 months after stopping dCF. Three patients have developed second malignancies. One patient developed stage IA Hodgkin's disease 70 months off therapy and also had recurrence of basal and squamous carcinoma of the skin, which had been present before dCF treatment. Two other patients had skin malignancies: a basal cell carcinoma 5 years posttreatment and multiple basal cell and squamous carcinoma of the skin in the second patient beginning 4 years after therapy. All of the above patients were greater than 64 years of age at the time their skin carcinomas developed. All of these

malignancies were successfully treated, and all patients are currently free of disease, excluding the only patient who died postremission. The median survival from the initiation of treatment is 93 months (range, 63 to 116 months).

DISCUSSION

Since the initial description by Bouroncle et al in 1958, hairy cell leukemia has been recognized as a disease with a varying natural history.^{9,10} Some patients go for years without needing treatment, whereas others develop progressive pancytopenia and require therapy.^{9,11} The median survival from diagnosis in several descriptive series ranges from 53 to 70 months, with the cause of death often due to infection.^{9,12} Before 1980 the only effective therapy was splenectomy, and in patients with minimal bone marrow disease, it significantly prolonged survival.¹³⁻¹⁵ However, patients with marked bone marrow involvement often developed progressive disease after splenectomy and subsequently die of disease-related complications.¹⁶

The introduction of new treatments for hairy cell leukemia has markedly changed the management of this disease, but it is yet unclear how much these new treatments affect long-term survival.^{2,7,17} In this report, we have documented that dCF treatment can produce both long-term survival and treatment-free survival in a group of patients with advanced hairy cell leukemia. Moreover, despite prior concerns about long-term susceptibility to infectious complications as a result of dCF treatment, our patients have been remarkably free of such problems.

The development of secondary malignancies after dCF has also been proposed as a potential problem. So far, there is not a marked increase over expected malignancies in this population. This contrasts with observations in a group of patients with hairy cell leukemia treated with interferon. At a 10-year follow up, 7 of 69 patients had developed either solid tumors or lymphoproliferative and hematologic malignancies.¹⁸

The incidence of skin malignancies in our patients may reflect the incidence seen in this age group as well as prior predisposition, as one of the patients had basal cell and squamous cell carcinoma present before dCF treatment. However, since skin malignancies are increased after immunosuppressive therapy,^{19,20} careful observation of all patients after dCF for skin lesions will be necessary to determine the role dCF therapy plays in their development.

With the success of dCF, our initial hope was that this treatment would produce cures in a significant number of our patients. However, the number of relapses that already have occurred suggests that hairy cell leukemia may be similar to other low grade lymphoproliferative disorders, where long-term survival is produced but recurrent treatment is necessary. It is difficult to predict at this time whether any of the patients who have not yet relapsed are cured of disease. We have compared our experience with the published data concerning response after treatment with either interferon or 2-CdA. Interferon rarely induces CR, and retreatment is often necessary.^{21,22} In one series with long-term follow up, 90% of patients were alive at 4 years, with almost half the

patients needing retreatment by 25 months.²² Furthermore, a prospective randomized study has shown that dCF produces a significantly higher number of CRs compared with interferon. In addition, the relapse-free survival after dCF treatment is markedly increased over that observed after interferon therapy.²³

Although 2-CdA induces a high percentage of CRs in 78% to 85% of patients,^{4,7,24} there are few studies with long-term follow-up. A 20% relapse rate with a median follow-up time of 16 months has been reported recently,²⁵ although bone marrow biopsies were not performed on a consistent basis after remission, which may lead to underestimating the number of relapses. Further observations will be necessary to determine whether the high CR rate translates into the prolonged survival rate that we have already seen after treatment with dCF.

The optimal approach to advanced hairy cell leukemia is still unclear, and determining the best approach will require at least a 10- to 15-year perspective. However, dCF has helped change advanced hairy cell leukemia from a fatal illness to a manageable one.

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