An Investigation of 2'-Deoxycoformycin in the Treatment of Cutaneous T-Cell Lymphoma

By Michael R. Grever, Emil Bisaccia, Dwight A. Scarborough, Earl N. Metz, and James A. Neidhart

We have investigated the use of 2'-deoxycoformycin (DCF), a potent inhibitor of adenosine deaminase (ADA), in the treatment of 4 patients with advanced mycosis fungoides (MF). Since DCF has demonstrated an adverse effect in vitro and in vivo on the survival of leukemia T-cell lines, it appeared reasonable to examine its effect in patients with advanced cutaneous T-cell lymphoma. A total of 8 courses of DCF were given to the 4 patients. Since this study was part of an ongoing phase I investigation, each patient received a fixed dose (varying from 4 mg/sq m to 10 mg/sq m daily for 3 consecutive days) on a 28-day schedule. One patient had reversible renal insufficiency. Three patients had reversible myelosuppression. Two patients had a complete remission of disease for 7 + and 9 + mo., respectively. Two additional patients had partial remissions for 4 and 9 mo., respectively. We concluded that effective antitumor activity in advanced MF can be achieved with DCF at doses that may not be associated with prohibitive toxicity. We would encourage further investigation of this agent in patients with advanced cutaneous T-cell lymphoma.

MYCOSIS FUNGOIDES (MF) is an uncommon malignant disorder best characterized as a cutaneous T-cell lymphoma. Although the natural history of this disease may be variable, MF associated with skin tumors, lymph node involvement, or hepatosplenomegaly has a poor prognosis.

Previous attempts to utilize single agents, combination chemotherapy, or combined modality therapy (radiation and chemotherapy) for patients with advanced stages of the disease have been palliative, but survival remains essentially unchanged.

2'-Deoxycoformycin (DCF), a potent inhibitor of the enzyme adenosine deaminase (ADA), has been investigated in phase I clinical trials for its potential use as an anticancer agent. Clinical investigation to date has demonstrated impressive tumor cell kill in a number of patients with T-cell malignancies. Some activity was reported in 2 patients with MF receiving DCF during phase I trials. Although the first phase I clinical trial of this agent in England revealed little drug toxicity, the initial investigations of this agent in the United States utilizing the same dose of the drug demonstrated considerable toxicity. Our recent phase I investigation of DCF utilizing lower doses clearly demonstrated that this agent is not only well tolerated but has activity in patients with MF. The clinical experience in treating four patients with advanced MF and DCF forms the basis for this report.

MATERIALS AND METHODS

Patients with advanced MF referred to the Ohio State University Hospital were considered for the DCF protocol if they fulfilled the eligibility criteria for the phase I study. All patients had a pathologic diagnosis of MF confirmed by biopsy of skin disease. All patients had a poor prognosis as evidenced by extensive plaque disease of the skin, skin tumors, lymph node involvement, or hepatosplenomegaly. Patients were fully informed of the experimental nature of this protocol and agreed in writing to participate.

Specific characteristics of the patient population treated are presented in Table 1. Each patient was evaluated with a complete history and physical examination, including mapping of the skin lesions with photographic documentation of skin involvement. A complete blood count, including a determination of the percentage of atypical lymphocytes in the peripheral smear, was made prior to therapy. Baseline liver and renal function studies were also obtained. Lymph node biopsy was performed when appropriate. Bone marrow biopsy was obtained prior to therapy in patients with abnormal peripheral blood counts.

The DCF was obtained from the Investigational Drug Branch of the National Cancer Institute, Bethesda, Md. The use of the agent was in accordance with an approved phase I protocol calling for escalation of dose level after every three patients. Patients with MF who were included in this study were entered sequentially with other patients with solid tumors. Therefore, the doses that each patient received varied. Each patient received a specific dose on a predetermined schedule. The initial dose for this investigation started at 6 mg/sq m/day, days 1–3. The first patients with MF were entered on this study at doses of 8 mg/sq m/day, days 1–3 (patients 1 and 2). Patient no. 3 was entered at 10 mg/sq m/day, days 1–3. Since objective responses were observed without prohibitive toxicity, a lower dose was examined to determine the lowest effective dose. Patient no. 4 entered the study at the final dose level 4 mg/sq m/day, days 1–3. Therefore, patient no. 4 received the lowest dose. Dose escalation for an individual patient was not allowed on this particular protocol. Courses were repeated at 28-day intervals if the patient had recovered from toxicity encountered from the previous course. The initial plan was to give a minimum of 3 courses to each patient, but concerns of cumulative toxicity generated during the early phase I studies prompted early cessation of therapy in two patients. Patients were closely monitored for hematologic, hepatic, ophthalmologic, and renal toxicity.

Patients were evaluated monthly for evidence of clinical response. A complete remission was defined as disappearance of all evidence of MF for a minimum of 4 wk and was confirmed by careful physical examination.
Table 1. Clinical Data

<table>
<thead>
<tr>
<th>Patient/ Age</th>
<th>Clinical Finding</th>
<th>Previous Treatment</th>
<th>Drug Administration</th>
<th>Adenosine Deaminase Inhibition</th>
<th>Observed Response/ Duration Response</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/40</td>
<td>Plaque stage with palpable lymphadenopathy.* Mild splenomegaly. Peripheral smear demonstrated 66% atypical lymphocytes (T2N1B1M0)</td>
<td>Topical steroids</td>
<td>8 mg/sq m i.v. push days</td>
<td>100% Complete resolution of skin lesions, lymphadenopathy, and splenomegaly. Peripheral smear reverted to a normal differential. Duration 9+ mo</td>
<td>Marked granulocytopenia and thrombocytopenia. Pretreatment bone marrow showed marked myeloid hypoplasia.</td>
<td></td>
</tr>
<tr>
<td>2/30</td>
<td>Extensive plaques with skin tumors and lymphadenopathy* (T1N1B1M0)</td>
<td>Topical steroids</td>
<td>8 mg/sq m i.v. push days</td>
<td>100% Complete resolution of all disease. Duration 7+ mo</td>
<td>Mild reversible granulocytopenia nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>3/63</td>
<td>Extensive plaques and lymphadenopathy† (T1N1B1M0)</td>
<td>Topical steroids</td>
<td>10 mg/sq m i.v. push days</td>
<td>100% Complete resolution of lymphadenopathy, 80% resolution of skin lesions. Duration 9 mo</td>
<td>Mild reversible granulocytopenia, nausea, and vomiting</td>
<td></td>
</tr>
<tr>
<td>4/82</td>
<td>Extensive plaques, recurrent tumor (T2N1B1M0)</td>
<td>Radiation, topical nitrogen mustard, and topical steroids</td>
<td>4 mg/sq m i.v. push days</td>
<td>60% Complete resolution of tumors; 90% resolution of skin lesions. Duration 4 mo</td>
<td>Mild reversible conjunctivitis and nephrotoxicity, fever, nausea and vomiting</td>
<td></td>
</tr>
</tbody>
</table>

*Lymph node demonstrated dermatopathic changes that consisted of reactive changes with many germinal centers demonstrating immunoblasts, plasma cells, associated with vascular proliferation.
†Lymph node demonstrated atypical hyperplasia including bizarre interfollicular infiltrates of large immunoblastic cells with mitoses present.

RESULTS

The data in Table 1 indicate that four patients received a total of 8 courses of DCF. The lymphadenopathy in all patients resolved following administration of this drug. Patients 1 and 2 achieved a complete remission after receiving 1 and 3 courses of the drug, respectively, at a dose of 8 mg/sq m/day. The other 2 patients achieved partial remission with complete resolution of their lymphadenopathy and greater than 80% clearing of their skin plaques (see Fig. 1). The two patients with complete remission have demonstrated no progression of disease since completing the administration of the DCF. The duration of these remissions varies from 4 to 9+ months. Patient 3 had a substantial partial remission (Fig. 1) after 3 courses, followed by a plateau in response. She received several additional doses of the agent followed by subsequent progression of skin lesions (10% body surface area) after 9 mo.

The toxicity associated with the administration of these agents is also indicated in Table 1. Patient 4 received one course of DCF at the lower dose of 4 mg/sq m/day. This patient had an initial serum creatinine of 1.0 mg/dl before treatment. Following drug administration, his serum creatinine briefly rose to 4 mg/dl. Within a 2-wk period, with conservative medical management, the serum creatinine had returned to a normal value. During the time that the serum creatinine was elevated, he had mild conjunctival inflammation, fever, nausea, and diarrhea. Although all of his symptoms cleared completely within 2 wk, the decision was made to hold further therapy unless his disease progressed.

The other three patients, who received higher doses of DCF, had mild nausea and vomiting but no nephrotoxicity. Patients 2 and 3 had moderate leukopenia, which was temporally related to the administration of the drug and was not complicated by infection. Patient
I developed significant leukopenia after administration of the drug, but had a low granulocyte count before treatment. A bone marrow biopsy obtained before treatment in this patient showed myeloid hypoplasia. At the nadir of his myelosuppression, his absolute granulocyte count was 400/cu mm with a platelet count of 24,000/cu mm. While this patient is not strictly evaluable for hematologic toxicity, there was a reversible decrease in both the absolute granulocyte count and platelet count. Since this patient remained in complete remission following a single course of the agent, a decision was made to follow him rather than to proceed with additional therapy.

Those patients who received the higher dose of the drug had complete inhibition of their peripheral blood buffy coat ADA following the administration of the DCF. The ADA activity in the buffy coat had recovered prior to initiation of the second course of chemotherapy. The patient who received the lowest dose of DCF had a definite decrease in the ADA activity, but inhibition was incomplete.

**DISCUSSION**

2'-Deoxycoformycin has been investigated in several phase I trials. The dose chosen for most of the initial investigations (10 mg/sq m/day, i.v. push, days 1–5) was based on an earlier report that had failed to demonstrate serious toxicity. In contrast, the studies in the United States documented that significant toxicity was observed at that dose. Central nervous system abnormalities, including confusion and seizures, renal insufficiency, elevation of liver enzymes, conjunctival inflammation, and fever, were reported following the administration of this agent at a dose of 10 mg/sq m for 5 days. In the initial studies, unequivocal improvement in several patients with far advanced lymphoproliferative malignancy encouraged investigators to pursue further studies with this agent. Efforts to define the biochemical mechanism underlying the clinical toxicity were initiated.

We investigated the biochemical alterations that occurred in the circulating erythrocytes of patients treated with this agent. The clinical toxicity was temporally correlated with major perturbations of the nucleotide pools in erythrocytes. An accumulation of dATP and a depletion of ATP correlated with onset of clinical toxicity. Resolution of toxicity was associated with reversal to normal nucleotide concentrations. These changes in the nucleotide content of erythrocytes were also reflected in parenchymal organs (liver, spleen, and kidney) of two patients who expired. We suspected that the intracellular accumulation of dATP and the depletion of ATP might explain the observed clinical toxicity and sought to investigate the use of lower doses that would not be associated with prohibitive toxicity.

2'-Deoxycoformycin has significant renal excretion, and in patients with pretreatment renal insufficiency,
toxicity may be enhanced. We have, therefore, restricted the administration of this agent to patients with normal renal function. All individuals in this study had normal pretreatment renal function. One elderly patient (patient 4) with a normal baseline creatinine and urinary bladder obstruction developed transient elevation of his serum creatinine following administration of a low dose (4 mg/sq m/day for 3 days) of this agent. No other patient, however, entered on the current phase I study at that low dose developed renal insufficiency. Inhibition of ADA in the present study was associated with serious myelosuppression in one patient with pretreatment myeloid hypoplasia. Phase I studies are primarily designed to evaluate acute toxicity. Long-term administration of 2'-deoxycoformycin may be associated with other adverse effects. Since ADA deficiency in children is associated with a severe combined immunodeficiency disease, it is conceivable that the long-term administration of this agent may predispose patients to the consequences of an incompetent immune system.

There is a biochemical rationale for utilizing this agent in MF. DCF has demonstrated an adverse effect in vitro and in vivo on the survival of leukemic T-cell lines. The proposed mechanisms of antitumor activity have included an intracellular accumulation of either dATP or S-adenosylhomocysteine, both of which could interfere with cell proliferation. Although the patients treated in this study had not received prior systemic therapy and constituted a relatively favorable group, the preliminary response rate and duration appear to be superior to other studies of single agents. The present study demonstrates that effective antitumor activity can be achieved at doses of DCF that inhibit ADA but are not associated with irreversible clinical toxicity. Careful biochemical monitoring in expanded phase II investigations will provide additional information about the utility of this drug in the treatment of this uncommon malignancy.

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REFERENCES

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