2-Chlorodeoxyadenosine: An Active Agent in the Treatment of Cutaneous T-Cell Lymphoma

By Alan Saven, Carlos J. Carrera, Dennis A. Carson, Ernest Beutler, and Lawrence D. Piro

Cutaneous T-cell lymphomas are disfiguring malignant lymphoproliferative disorders for which standard therapy has been principally palliative. 2-Chlorodeoxyadenosine (2-CdA), a new purine analogue resistant to degradation by adenosine deaminase that has substantial activity against lymphoid neoplasms, was administered to 16 patients with cutaneous involvement by T-cell lymphoma. All patients had failed topical treatment modalities and/or systemic therapies. Fifteen patients were evaluable; one patient was not evaluable due to incomplete therapy and follow-up. The overall response rate was 47%. Three of 15 patients (20%) achieved complete responses and four of 15 patients (27%) achieved partial responses. The median duration of response was 5 months. One patient remains in unmaintained complete remission at 52+ months. Therapy was well tolerated. Myelosuppression was the principal toxicity encountered, occurring in 8 of 15 (53%) patients. 2-CdA is an effective new agent for the treatment of cutaneous T-cell lymphoma and warrants further study both as a single agent and in combination regimens.

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MATERIALS AND METHODS

Eligibility. All patients with a skin biopsy confirmatory for mycosis fungoides or Sezary syndrome, and patients with a peripheral T-cell lymphoma14 and either primary or prominent cutaneous involvement were eligible for the study. T-cell phenotype was documented by cell marker studies performed on frozen tissue. Monoclonal antibodies were tested against the T-lymphocyte antigens CD2, CD3, CD4, CD5, CD7, and CD8. Ki-1+ anaplastic large-cell lymphoma and human T-cell lymphotropic virus (HTLV)-associated lymphomas were ineligible. Eligible patients had failed topical and/or systemic therapy and had an estimated life expectancy of more than 3 months. Adequate renal and hepatic function were documented. Patients were required to have measurable disease documented by skin examination, bone marrow biopsy, or by computerized axial tomographic scanning. All patients were required to be over 18 years of age. A remote history or a concomitant diagnosis of another lymphoproliferative disorder were not exclusion criteria. The study was approved by our institutional review board and written informed consent was obtained before the initiation of therapy.

Drug therapy. 2-CdA was synthesized and purified as described,15 or obtained from Ortho Pharmaceutical (Raritan, NJ) and recrystallized before use. 2-CdA was supplied to the pharmacy as a 0.1% solution (1 mg/mL) of pyrogen-free 2-CdA in sterile 0.9% NaCl. The desired dose (0.05 to 0.15 mg/kg/d) was added to 500 mL of 0.9% NaCl solution and administered by continuous intravenous infusion for 7 days. Patients were treated at 4-week intervals until maximal response was achieved or prohibitive toxicity encountered, and then observed.

Response criteria. All patients were evaluated with a complete history and physical examination, multiple photographic documents of cutaneous involvement, complete blood cell count with differential, chest x-ray, bone marrow aspiration and biopsy, and...
computerized axial tomographic scans of the chest, abdomen, and pelvis. Lymph node and skin biopsies were performed when appropriate, and repeated when necessary to confirm the response status. After therapy, patients were examined monthly to assess their clinical response. A complete remission required the disappearance of all detectable lymphoma for a minimum of 1 month as determined by examination, imaging studies, and biopsy when necessary. A partial response was defined as at least a 50% reduction in the sum of perpendicular measurements of malignant lesions lasting at least 1 month. Less than a 50% reduction of the cutaneous and visceral disease was defined as no response. Progressive disease was defined as a 25% or greater increase in the sum of perpendicular measurements or the development of any new malignant lesions.

Toxicity criteria. Significant hematologic toxicity was determined by a greater than 50% decrease from the pretreatment value, grade 3 being a 50% to 74% decrease and grade 4 a greater than 75% decrease. This hematologic toxicity grading scale with degree of toxicity based on a percentage of the pretreatment values was selected to more accurately assess myelotoxicity in patients with preexistent cytopenias. Nonhematologic toxicities were monitored and assessed according to standardized criteria, with grade 3 or greater toxicity being considered significant.

Statistical methods. Fisher's exact test was used for the comparison of proportions. All reported P values are two-sided.

RESULTS

Study Populations

Sixteen patients with cutaneous T-cell lymphoma were enrolled (Tables 1 and 2). Six patients with histologically confirmed mycosis fungoides and three patients with Sezary syndrome, all with a T-helper cell phenotype (CD4), were treated. Seven patients were assigned to the nonmycosis fungoides group because of histologic and T-phenotypic differences. Included in this disease category were six patients with a peripheral T-cell lymphoma, four being T-immunoblastic lymphomas, and a single patient with a T-suppressor cell (CD8) lymphoma. There were 11 men and five women. The median age was 66 years (range, 47 to 86). Two patients had stage I, seven had stage II, two had stage III, and five had stage IV disease using the National Cutaneous T-Cell Lymphoma Workshop staging classification. The median pretreatment duration was 2 years (range, 0.5 to 14). Patient accrual was over a 5-year period, from January 1986 to December 1990; seven patients were enrolled in 1986, two in 1987, one in 1988, and five in 1990. Forty courses of 2-CdA were administered to these 16 patients. A single patient elected not to complete his first course of 2-CdA therapy and was therefore not evaluated because of incomplete therapy and follow-up data.

Responses and Response Duration

Overall, 7 of 15 (47%) patients responded; the 95% confidence interval for this proportion ranged from 21.7% to 80.1% (Tables 1 and 2). The median duration of response was 5 months. Three of 15 patients (20%) achieved complete responses. Two of the patients achieving complete remission were stage IIIB at the initiation of treatment, and one was stage III. A single patient with a peripheral T-cell lymphoma and an unusual T-cell immunohistochemical profile currently remains in prolonged, unmaintained complete response (52+ months). Cutaneous biopsy in this patient demonstrated abnormal helper T cells lacking the pan-T antigens CD2, CD5, and CD7. The cutaneous response of this patient is shown in Fig 1. A subsequent patient with a T-immunoblastic lymphoma achieved a complete remission for 29 months, at which time she developed abdominal symptoms and underwent exploratory laparotomy. At laparotomy she was found to have a CALLA+, B-cell, diffuse mixed malignant lymphoma. The lymphoma appeared to arise from the transverse colon, with secondary invasion of the small bowel and anterior abdominal wall. The third patient, who had mycosis fungoides, achieved a complete response of 1.5 months duration. He had a remote history of stage IA mixed cellularity Hodgkin's disease treated by definitive irradiation with no subsequent disease recurrence.

Four of 15 patients (27%) achieved partial responses, ranging from 1.5 to 38 months in duration. Two of these patients had mycosis fungoides and two had nonmycosis fungoides cutaneous T-cell lymphoma. A single patient with suppressor T-cell skin infiltration had a partial re-

<table>
<thead>
<tr>
<th>Age/Race/Sex</th>
<th>Stage</th>
<th>Cumulative 2-CdA mg/kg/d × 7 days</th>
<th>Response</th>
<th>Duration (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55/W/F</td>
<td>IA (T(NmMxB))</td>
<td>XRT, UVA</td>
<td>0.30 (3)</td>
<td>NR</td>
</tr>
<tr>
<td>62/W/M</td>
<td>IB (T(NmMxB))</td>
<td>UVA</td>
<td>0.30 (3)</td>
<td>NR</td>
</tr>
<tr>
<td>61/W/M</td>
<td>IB (T(NmMxB))</td>
<td>XRT, Top (3), Sys (1)</td>
<td>0.40 (3)</td>
<td>PR</td>
</tr>
<tr>
<td>61/W/F</td>
<td>IB (T(NmMxB))</td>
<td>XRT, UVA, Top (2)</td>
<td>0.10 (1)</td>
<td>NR</td>
</tr>
<tr>
<td>66/W/F</td>
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<td>XRT, UVA, Sys (2)</td>
<td>0.20 (2)</td>
<td>PR</td>
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<tr>
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<td>0.80 (6)</td>
<td>CR</td>
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<tr>
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<td>Sys (2)</td>
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<td>NR</td>
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<tr>
<td>80/W/M</td>
<td>NVC (T(NmMxB))</td>
<td>Top (1)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Total: 3/8 (38%) response rate</td>
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Abbreviations: XRT, radiation therapy; Top, topical chemotherapy (no. of agents); UVA, UV light A in combination with psoralens; Sys, systemic chemotherapy (no. of regimens); CR, complete response; PR, partial response; NR, no response; NE, not evaluable.

*Single patients with Sezary syndrome.
†Previously treated stage IA mixed cellularity Hodgkin's disease.
spontaneous response of 38 months. He had bone marrow involvement, abdominal lymphadenopathy, and skin involvement before the initiation of treatment. The other partial responses lasted from 1.5 to 5 months. Seven of 15 (47%) patients had no response, while one patient with concomitant stage A, B-cell chronic lymphocytic leukemia had progressive cutaneous disease despite a greater than 50% decrement in his absolute lymphocyte count. A patient with Sezary syndrome did have areas of skin clearing without strictly meeting the criteria for a partial response. All patients who did not respond to therapy died within 3 to 7 months of completion of the trial.

Three of the six patients (50%) with peripheral T-cell lymphoma responded, including two of the four patients with the T-immunoblastic lymphoma subtype. The median pretreatment duration in the responding patients was 2 years (range, 0.5 to 11) versus 1.8 years (range, 0.75 to 14) in the nonresponders. There were no differences in the histories of prior treatment responses between the responding and nonresponding patient groups.

Toxicity

General. No nausea or vomiting, alopecia, or hepatic or renal insufficiency occurred in any patient as a result of 2-CdA treatment.

Bone marrow suppression. Eight of 15 (53%) patients experienced myelosuppression as previously defined. Of these eight patients, four had isolated neutropenia (three with transient grade 3 neutropenia, and one with transient grade 4 neutropenia), one patient experienced isolated transient grade 3 thrombocytopenia with no episodes of clinical bleeding, and three patients developed panmyelopenia.

Of the three patients who developed pancytopenia, two had Sezary syndrome. One of these patients with Sezary syndrome and a pretreatment marrow involved with lymphoma developed pancytopenia along with disappearance of the lymphoma in the marrow. Before receiving 2-CdA, she had been treated with aggressive multiagent chemotherapy, and marrow cellularity was estimated at 10%. She was one of two patients whose platelet count fell below 40,000/μL. The third patient with pancytopenia had mycosis fungoides and a previous history of Hodgkin's disease treated with irradiation.

Myelosuppression was more common in those patients with mycosis fungoides than in the nonmycosis fungoides group of cutaneous T-cell lymphoma patients. Six of eight patients developed significant leukopenia in the mycosis fungoides group versus one of seven patients in the nonmycosis fungoides group (P = .04, Fisher exact test) (Table 3). Four of eight patients experienced thrombocytopenia in the mycosis fungoides group versus none in the nonmycosis fungoides group (P = .08). Although the small number of patients in each subgroup does not permit accurate analysis, in the mycosis fungoides group, stage and prior therapy did not appear to affect the frequency of leukopenia, but may have influenced the incidence of thrombocytopenia; both for patients with stages I and II disease and for those not previously treated with systemic therapy, one of four patients developed thrombocytopenia versus three of four patients for both stages III and IV disease and also for patients with a prior exposure to systemic therapy.

Infectious complications. Three of 15 (20%) patients had infectious complications. One of these patients, who experienced transient grade 3 neutropenia, had extensive lymphomatous involvement of the perineal skin. She developed skin breakdown and secondary skin infection when leukopenic. Before 2-CdA chemotherapy, computerized axial tomographic scans of the chest had shown multiple, calcified nodular lesions. She had a remote history of a thoracotomy for pulmonary coccidioidomycosis. Because of negative pretreatment coccidioidomycosis serologic studies and stable chest x-ray findings, it was felt to be inactive. Three months following therapy with 2-CdA, she was diagnosed with disseminated coccidioidomycosis. It was not known whether this represented reactivation or a new primary infection, as she lived in an endemic area for coccidioidomycosis.

A second patient with extensively pretreated Sezary syndrome, who developed pancytopenia, was found to have
disseminated candidiasis at autopsy, and the third patient who did not experience myelosuppression developed Staphylococcus aureus bacteremia from a cutaneous source.

**DISCUSSION**

2-CdA is an adenosine deaminase-resistant purine analogue that exerts its cytotoxic effects independent of cell cycle. Perhaps this is the reason that it has been so effective in clinical trials for low-grade B-cell lymphoid neoplasms such as chronic lymphocytic leukemia, hairy cell leukemia, and low-grade lymphoma. Cutaneous T-cell lymphomas, although T-cell in origin, are often low-grade lymphoid neoplasms with low-growth fractions that, as shown here, appear sensitive to treatment with 2-CdA. Although 2-CdA shows high activity clinically in B-cell lymphoproliferative disorders, in vitro data with B- and T-lymphoblastoid cell lines had suggested that T cells may in fact be more susceptible than B cells to 2-CdA treatment. The in vivo data presented here confirm that T-cell diseases are responsive to 2-CdA treatment.

The relatively high response rates (47%) achieved in this single-agent pilot study, some being complete and durable,
demonstrate that 2-CdA is an active agent in the treatment of T-cell lymphomas with cutaneous involvement. Although the number of patients in this study is too small for meaningful subset analysis, patients with mycosis fungoides experienced greater myelotoxicity following 2-CdA administration than patients with nonmycosis fungoides cutaneous T-cell lymphoma. The toxicity spectrum of 2-CdA observed in this trial is similar to that previously reported with other diseases, principally myelosuppression. In trials of 2-CdA in chronic B-cell neoplasms, myelosuppression was primarily evident as thrombocytopenia with only mild neutropenia and without significant suppression of erythropoiesis. However, in this trial, 3 of 15 (20%) patients experienced pancytopenia. Two of these patients had Sezary syndrome, had been extensively treated before entry into the trial, and had bone marrow involvement at the time of treatment. The broader nature of the myelosuppression experienced by those patients with T-cell diseases is different from that seen in patients with B-cell diseases. This may be due to differences in the underlying diseases being of T-lymphocyte lineage and possibly differences in lymphocyte subset sensitivity in vivo. Two of the three patients who developed infectious complications experienced myelosuppression. Like 2'-deoxycoformycin, flow cytometric studies in patients with hairy cell leukemia have confirmed that 2-CdA is immunosuppressive, and this could conceivably have contributed to the disseminated fungal infections and the emergence of a new CALLA+ B-cell lymphoma in one patient, although specific parameters of immune function were not studied in this patient group.

The responses and toxicities induced by 2-CdA in cutaneous T-cell lymphoma compare favorably with the nucleosides fludarabine and 2'-deoxycoformycin. Six of 31 (19%) with advanced mycosis fungoides who received fludarabine achieved responses. Toxicity included severe myelosuppression with two fatalities from sepsis, and single patients each developed pulmonary fibrosis and neurotoxicity. In 1983, 2'-deoxycoformycin, at variable doses, was administered to four patients with advanced mycosis fungoides. Two patients achieved a complete response and two patients a partial response. Toxicity included myelosuppression, nausea, vomiting, and renal insufficiency. More recently, 2'-deoxycoformycin was administered to patients with refractory lymphoma in a cooperative group study. Four of eight patients with cutaneous T-cell lymphoma obtained a partial response; three of these patients developed severe myelosuppression that was associated with life-threatening infections. These data suggest that 2-CdA is an active nucleoside against cutaneous T-cell lymphoma, although further studies with larger numbers of patients will be needed to clearly define the role of this agent for affected patients. Myelosuppression remains a concern with all the nucleosides in the treatment of cutaneous T-cell lymphoma. The concomitant administration of growth factors may provide an opportunity to ameliorate these effects.

Future studies will use 2-CdA in combination with other active chemotherapeutic agents, having nonoverlapping toxicities, and biologic response modifiers. Alternating cycles of 2'-deoxycoformycin and interferon-α has already been successfully used in the treatment of patients with advanced mycosis fungoides and suggests that 2-CdA in combination with biologic agents might represent a successful treatment strategy. We hope that with new active agents like 2-CdA effective in the treatment of cutaneous T-cell lymphoma, response rates might be able to approximate those already achieved with intermediate-grade, B-cell, malignant non-Hodgkin's lymphomas.

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