2-Chlorodeoxyadenosine Activity in Patients With Untreated, Indolent Non-Hodgkin’s Lymphoma

By Alan Saven, Susan Emanuele, Michael Kosty, James Koziol, Douglas Ellison, and Lawrence Piro

Based on the encouraging results of the use of 2-chlorodeoxyadenosine (2-CdA; cladribine) in patients with advanced, low-grade lymphomas resistant to conventional therapy and the acceptable toxicity profile encountered, we conducted a phase II trial of 2-CdA in patients with untreated indolent lymphomas. Twenty-eight patients with untreated low-grade lymphomas were given 2-CdA at 0.1 mg/kg/d as a 7-day continuous infusion every 28 to 35 days. A total of 89 courses, median of three courses per patient, of 2-CdA were administered. Seventeen men and 11 women with a median age of 58 years were treated. Fifteen patients had diffuse small lymphocytic (8 with plasmacytoid features), 10 had follicular small cleaved-cell, and there were single patients with monocytoid B-cell, mantle cell and mucosa-associated lymphoid tissue (MALT) lymphoma histologies. All 28 patients were evaluable for toxicity and 26 were evaluable for response. Nine (35%) patients (4 with diffuse small lymphocytic, 3 with follicular small cleaved-cell, 1 with mantle cell, and 1 with MALT lymphoma) achieved a complete response, and 14 (54%) patients (8 with diffuse small lymphocytic, 5 with follicular small cleaved-cell, and 1 with monocytoid B-cell lymphoma) achieved a partial response, for an overall response rate of 88%. The median response duration was 10 months (range, 3 to 44+). Myelosuppression was the principal toxicity. Actuarial survival at 60 months from initial diagnosis was 60% (95% confidence interval, 35% to 82%) and at 48 months from treatment onset was 82% (95% confidence interval, 39% to 83%). These results establish the major activity of 2-CdA in patients with untreated indolent lymphomas, especially those with the diffuse small lymphocytic subtype.

LOW-GRADE non-Hodgkin’s lymphomas (NHLs) are indolent B-cell neoplasms that are usually not treated in their early stages because standard therapy is not curative. The median survival of patients with these histologies is 8 to 10 years. Therapy is instituted for rapid disease progression, B-symptomatology, cytopenias related to marrow replacement by disease, or disease threatening the function of a vital organ. Treatment usually consists of an alkylating agent, with or without prednisone, inducing responses in 65% of untreated patients. A randomized trial of initial intensive chemotherapy versus no therapy conducted at the National Cancer Institute showed a complete remission rate of 75%, but at a median follow-up of 7 years, there were no significant survival differences between the randomized arms. The majority of patients will eventually relapse or progress after an initial response to treatment. There is no standard salvage treatment once patients develop refractoriness to alkylating agents.

2-Chlorodeoxyadenosine ([2-CdA], cladribine, Leustatin) is a newer purine analog resistant to deamination by adenosine deaminase, an enzyme critical in purine metabolism. 2-CdA is unique among conventional antimitabolites being cytotoxic to both resting and proliferating lymphocytes. This property of 2-CdA likely confers it a unique advantage over standard therapies when treating neoplasms with low-growth fractions, such as the low-grade lymphomas. We have reported on 40 patients with low-grade lymphoma, having failed a median of three prior chemotherapy regimens, who were treated with 2-CdA. An overall response rate of 43% was achieved, with eight (20%) patients experiencing complete responses and nine (23%) patients partial responses, with a median response duration of 5 months. 2-CdA has also been shown to have activity in the treatment of cutaneous T-cell lymphomas. Based on these encouraging results of the use of 2-CdA and the acceptable toxicity profile encountered, we initiated a phase II trial to study 2-CdA in patients with advanced stage, untreated indolent lymphomas.

MATERIALS AND METHODS

Eligibility criteria. Patients were eligible if they had a histologic diagnosis of low-grade NHL including the following subtypes: diffuse small lymphocytic, follicular small cleaved-cell, follicular mixed small cleaved-cell and large-cell, monocytoid B-cell, mantle cell, and mucosa-associated lymphoid tissue (MALT) lymphomas. Standard treatment indications were used, namely, rapid disease progression or bulky disease, B-symptomatology and cytopenias resulting from bone marrow involvement. Patients must have received no prior chemotherapy. Prednisone was permitted, at the lowest possible dose, to control either disease-related immune hemolysis or immune thrombocytopenia. Normal hepatic and renal functions were required, except in patients where lymphoma was the direct cause of the abnormality. Patients were required to be more than 18 years of age and have a 3-month or greater life expectancy. Institutional review board approval was obtained and all patients gave written informed consent.

Staging studies. All patients underwent a pretreatment history and physical examination, complete blood count with differential, chemistry panel that included renal and hepatic functions, serum immunoelectrophoresis and quantitative immunoglobulin level determinations, bone marrow aspiration and biopsy, and computerized axial tomographic (CT) scans of the chest, abdomen and pelvis. At maximum response and every 6 months in responding patients until disease progression, patients were reevaluated using the same diagnostic and imaging techniques.

Drug therapy. 2-CdA (cladribine, Leustatin) was supplied by...
Ortho Biotech (Raritan, NJ) and administered as 0.1 mg/kg/d 7-day continuous intravenous infusions every 28 to 35 days. Patients were treated as outpatients using a peripherally inserted central catheter and a CM-PCA pump (Pharmacia Deltec, St Paul, MN). When there was a greater than 50% reduction from pretreatment in the platelet count, further 2-CdA was withheld until the platelet count had achieved at least 75% of its pretreatment value or was >100 X 10^9/L. When the absolute neutrophil count was <1.0 X 10^9/L, 2-CdA treatment was held until the absolute neutrophil count was >1.0 X 10^9/L. No dose reductions were used in subsequent courses.

Four weeks after completion of the second course of 2-CdA, staging was repeated to assess response and thus subsequent therapy. In the presence of clinically evaluable disease demonstrating a response, further 2-CdA treatment was administered. In the absence of clinically evaluable disease, CT scans of previously abnormal areas of involvement, and if appropriate, a bone marrow examination, were repeated. If a complete response was achieved, the patient received no further 2-CdA and was observed. If a partial response was achieved, the patient was continued on therapy to determine the maximum response. If one to two courses of 2-CdA were administered beyond a partial response and there was no further improvement, this was considered the maximum response and treatment was discontinued. In the presence of protracted myelosuppression, no further 2-CdA was administered. A maximum of six courses of 2-CdA was permitted.

Response criteria. A complete response was defined as the absence of disease on physical examination, CT scans of the chest, abdomen and pelvis, and, if previously involved, bone marrow biopsy for greater than 4 weeks. The posttreatment bone marrow had less than 30% of nucleated cells being lymphocytes and no evidence of abnormal lymphoid infiltration. All lymph nodes had returned to normal size; splenomegaly and/or hepatomegaly must have fully resolved on CT scan. B-symptoms, if present, had abated.

A partial response was defined as a reduction by more than 50% of the sum of the products of the diameters of all measurable disease for more than 1 month. Any response less than that sufficient to qualify as a partial response was designated no response. Progressive disease was defined as a ≥25% increase in measurable disease.

Toxicity criteria. Standard criteria of the Eastern Cooperative Oncology Group (ECOG) were used for the evaluation of hematologic and nonhematologic toxicities. Grade III, IV, and V toxicities were considered significant.

Statistical methods. Fisher’s exact test was used for the comparison of proportions and the Kaplan-Meier method for estimating survival distribution.

RESULTS

Patient demographics. Twenty-eight consecutive patients with untreated indolent lymphomas entered the study between November 1989 and April 1993 (Table 1). Response evaluation was until April 1994. The median age of the 17 men and 11 women was 58 years (range, 36 to 81 years) and the median pretreatment duration was 6 months (range, 1 to 60 months). One patient had stage IIIA-E, 4 had stage IIIA, 18 had stage IV, and 5 had stage IVB disease. Fifteen patients had diffuse small lymphocytic (7 without plasmacytoid features and 8 with plasmacytoid features), and 10 had follicular small cleaved-cell NHL. There were single patients with monocytoid B-cell, mantle cell, and MALT lymphoma histologies, all of whom had followed an indolent course. A total of 89 courses of 2-CdA were administered with a median of 3 courses to each patient (range, 1 to 6 courses).

No patient had received prior alkylator treatment for low-grade lymphoma. One patient received steroids to ameliorate disease-related immune hemolysis and immune thrombocytopenia, and one patient had previously received a brief course of interferon therapy.

Responses and response duration. Of the 28 patients who were treated with 2-CdA, 26 were evaluable for response (1 patient with a prior history of an invasive scalp angiosarcoma died 3 weeks after one course of 2-CdA from massive hemoptysis complicating pulmonary metastases, and 1 patient moved to Europe after one course of 2-CdA and was lost to follow-up; both had diffuse small lymphocytic histologies), and all were evaluable for toxicity. Twenty-three (88%) achieved a response, with 9 (35%) patients achieving complete responses (95% confidence interval, 13% to 59%), and 14 (54%) patients achieving partial responses (95% confidence interval, 28% to 76%) (Table 2). The median duration of response was 10 months (range, 3 to 44+ months); 13 months for the complete responders (range, 8 to 44+ months), and 8 months for the partial responders (range, 3 to 36+ months). The median number of 2-CdA courses administered to achieve a complete response was 4 (range, 1 to 6 courses) and the median number of 2-CdA courses to achieve a partial response was 3.5 (range, 1 to 6 courses). Therapy was discontinued in the 14 patients who achieved a partial response because 5 patients demonstrated a lack of ongoing responsiveness to further 2-CdA therapy, 3 patients had persistent ECOG grade 2 neutropenia (absolute granulocyte count 1.0 to 1.5 X 10^9/L) or grade 2 thrombocytopenia (platelet count 50 to 90 X 10^9/L), 3 pa-
Table 2. Responses by Histologic Subtypes

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>No. of Patients</th>
<th>CR</th>
<th>PR</th>
<th>NR or PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse small lymphocytic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without plasmacytoid features</td>
<td>5</td>
<td>1</td>
<td></td>
<td>3 (5, 36+)</td>
</tr>
<tr>
<td>With plasmacytoid features</td>
<td>8</td>
<td>3 (23, 24, 43+)</td>
<td>5 (8, 8, 9, 24+, 34+)</td>
<td>0</td>
</tr>
<tr>
<td>Follicular small cleaved-cell</td>
<td>10</td>
<td>3 (12, 12, 44+)</td>
<td>5 (3, 3, 5, 10, 18)</td>
<td>2</td>
</tr>
<tr>
<td>Monocytoid B cell</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (8)</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1 (8)</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (13)</td>
</tr>
<tr>
<td>Overall response (%)</td>
<td>26</td>
<td>9</td>
<td></td>
<td>14 (54%)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; NR, no response; PD, progressive disease.

Patients had disease transformation, 1 patient had received the maximum 6 courses of therapy, 1 patient had progressive disease, and 1 patient declined further treatment.

Of the 5 patients with diffuse small lymphocytic lymphoma without plasmacytoid features, 1 (20%) achieved a complete response and 3 (60%) a partial response; of the 8 patients with diffuse small lymphocytic lymphoma with plasmacytoid features, 3 (37%) obtained a complete response and 5 (63%) a partial response; of the 10 patients with follicular small cleaved-cell lymphoma, 3 (30%) obtained a complete response and 5 (50%) a partial response; the 1 patient with monocytoid B-cell lymphoma achieved a partial response, the 1 patient with mantle cell lymphoma achieved a complete response, and the 1 patient with MALT lymphoma achieved a complete response.

Of the 9 patients who obtained complete responses, 2 remain in remission at 43+ and 44+ months. Seven patients have relapsed at a median of 12 months (range, 8 to 24 months); 4 have not required further therapeutic intervention, 1 was retreated with 2-CdA achieving a second response, and 2 died, 4 months and 28 months after having relapsed, respectively.

Of the 14 patients who obtained partial responses, 3 remain in remission at 24+, 34+, and 36+ months. Eleven patients have relapsed at a median of 7 months (range, 3 to 18 months); 3 subsequently underwent splenectomy and have not required further therapeutic intervention, 3 received alkylator-containing chemotherapy, 1 patient received fludarabine without response, 1 patient received radiation therapy, and 3 patients died from disease transformation.

The probability of freedom from relapse for responding patients at 36 months was 17% (95% confidence interval, 11% to 25%) (Fig 1).

Serial serum Ig levels. Of the 28 patients entered in the study, 12 (43%) had a monoclonal gammopathy, 4 with IgG κ, 7 with IgM κ, and 1 with IgM λ. Two patients had diffuse small lymphocytic without plasmacytoid features, 6 had diffuse small lymphocytic with plasmacytoid features, and 4 had follicular small cleaved-cell lymphomas. Their median pretreatment IgG level was 1,160 mg/dL with a range of 818 to 6,660 mg/dL (normal range, 720 to 1,690 mg/dL), and their median pretreatment IgM level was 1,790 mg/dL with a range of 394 to 6,510 mg/dL (normal range, 63 to 277 mg/dL). The median nadir IgG was 1,090 mg/dL (range, 865 to 1,443 mg/dL) and the median nadir IgM was 372 mg/dL (range, 132 to 2,600 mg/dL). In responding patients, the median nadir IgM level was achieved after 6 months and maintained during the 24 months of observation. There were no patients with normal pretreatment serum Ig levels who then developed hypogammaglobulinemia following 2-CdA treatment.

Toxicities. No patients experienced nausea, vomiting, alopecia, renal, hepatic, cardiac, pulmonary, or neurologic toxicity attributable to 2-CdA. As with other clinical trials of 2-CdA by continuous infusion for 7 days, myelosuppression was the principal toxicity occurring in 13 (46%) of patients.

Neutropenia was the most frequent hematologic toxicity (Table 3). Eight patients developed ECOG grade 3 neutropenia with an absolute granulocyte count 0.5 to 1.0 × 10^9/L, and two patients developed grade 4 neutropenia with an absolute granulocyte count <0.5 × 10^9/L. Three patients
developed ECOG grade 3 thrombocytopenia with a platelet count 25 to 50 × 10^9/L and one patient developed grade 4 thrombocytopenia with a platelet count <25 × 10^9/L. Two patients required red blood cell transfusional support, one of whom went on to receive two subsequent courses of 2-CdA with correction of the anemia.

One patient without hematologic toxicity was admitted for culture-negative fever, two patients developed dermatomal herpes zoster, and one patient was thought to have developed reactivation of prior hepatitis C infection.

**Transformation and survival.** These 28 patients have been followed-up for a median of 33 months (range, 2 to 52 months) after the administration of 2-CdA. Nineteen patients remain alive, eight patients have died and one patient was lost to follow-up. The actuarial survival from diagnosis to death was 25 months (range, 3 to 61 months) and the median time from 2-CdA treatment to death was 17 months (range, 2 to 41 months). Of the 8 patients who died, 3 had histologic evidence of disease transformation to a more aggressive lymphoma (Table 4). Among the 3 patients with disease transformation, before therapy 2 had follicular small cleaved-cell and 1 had diffuse small lymphocytic lymphomas, and all 3 had achieved brief partial responses following 2-CdA therapy. These 3 patients died despite the institution of multi-agent chemotherapy and/or radiation therapy. The probability of disease transformation at 5 years from diagnosis was 13% (95% confidence interval, 3% to 29%) (Fig 4) and the probability of disease transformation at 4 years from treatment onset was 12% (95% confidence interval, 2% to 27%) (Fig 5).

Of the 5 patients who died without histologic evidence of disease transformation, 3 patients (2 with diffuse small lymphocytic and 1 with follicular small cleaved-cell lymphoma) died from progressive disease, 1 of them 4 months after relapsing from a 2-CdA–induced complete response of 23 months duration. One patient died from metastatic sarcoma 1 month after receiving a single course of 2-CdA, and one patient with follicular small cleaved-cell histology died of disseminated nocardiosis 28 months after achieving a 2-CdA–induced complete response of 12 months, after having later received fludarabine and high-dose steroids for refractory immune hemolysis and thrombocytopenia.

**DISCUSSION**

We have previously reported on 40 patients with low-grade lymphomas who failed to respond to alkylator therapy, treated with 7-day continuous infusions of 2-CdA at 0.1 mg/kg/d. Of
Table 4. Survival-Deaths

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Pretreatment Histology</th>
<th>No. of 2-CdA Courses</th>
<th>Response to 2-CdA</th>
<th>Time From Diagnosis to Death (mo)</th>
<th>Time From Treatment to Death (mo)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diffuse small lymphocytic</td>
<td>3</td>
<td>PR (3)</td>
<td>29</td>
<td>13</td>
<td>Transformation-large cell lymphoma (FNA)</td>
</tr>
<tr>
<td>2</td>
<td>Follicular small-cleaved</td>
<td>4</td>
<td>PR (5)</td>
<td>25</td>
<td>23</td>
<td>Transformation-follicular large-cleaved</td>
</tr>
<tr>
<td>3</td>
<td>Follicular small-cleaved</td>
<td>5</td>
<td>PR (3)</td>
<td>21</td>
<td>12</td>
<td>Transformation-follicular large-cleaved</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse small-cleaved</td>
<td>1</td>
<td>PD</td>
<td>24</td>
<td>20</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>5</td>
<td>Diffuse small lymphocytic</td>
<td>5</td>
<td>CR (23)</td>
<td>34</td>
<td>33</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>6</td>
<td>Follicular small-cleaved</td>
<td>2</td>
<td>PD</td>
<td>9</td>
<td>6</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>7</td>
<td>Diffuse small lymphocytic</td>
<td>1</td>
<td>Unevaluable</td>
<td>3</td>
<td>2</td>
<td>Metastatic sarcoma</td>
</tr>
<tr>
<td>8</td>
<td>Follicular small-cleaved</td>
<td>2</td>
<td>CR (12)</td>
<td>61</td>
<td>41</td>
<td>Disseminated nocardiosis</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
<td>25 (3-61)</td>
<td>17 (2-41)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: FNA, fine needle aspiration.

These 40 patients, 6 with histologic evidence of evolution to higher-grade lymphomas, 8 patients (20%) experienced complete responses and 9 patients (23%) experienced partial responses for an overall response rate of 43% and a median duration of response of 5 months (range, 1 to 33+ months). Other investigators have documented similar response rates in this subset of lymphoma patients. Hoffman et al treated 21 alkylator-refractory low-grade lymphoma patients with a median of 2 courses (range, 1 to 5 courses) of 2-CdA, achieving an overall response rate of 9 (43%). The higher response rates and lower incidence of myelosuppression and infectious complications observed in this study of untreated patients contrasts with that study in which patients had received a median of 2 prior chemotherapeutic regimens (range, 1 to 7). Cerny et al treated 16 alkylator-failed patients, achieving an overall response rate of 12 (75%).

This is the first report establishing the response rates of 2-CdA in patients with untreated B-cell low-grade lymphomas. It should be noted that the histologic subtypes of patients included in this trial were different from other clinical studies of patients with low-grade lymphoma where follicular small cleaved-cell generally comprised approximately one half of the cases and follicular mixed and diffuse small lymphocytic lymphoma the remaining half. No patients with follicular mixed small cleaved-cell and large-cell histology, the low-grade lymphoma most responsive to combination chemotherapy, were treated in this trial. In this trial, actuarial survival at 60 months from initial diagnosis was 60%. Representative 5-year results of other clinical trials using various treatments for low-grade lymphomas yield survival rates of 60% to 82%. However, a direct comparison of results is difficult given the variability in histologic subtypes,
stages of disease and pretreatment duration, as well as the small numbers of patients treated.

The therapeutic strategy adopted in this study was aimed at minimizing the potential for cumulative myelosuppression and immunosuppression. Accordingly, the maximum number of 2-CdA courses was limited to six, and therapy was discontinued if there was significant protracted myelosuppression or a lack of ongoing responsiveness to treatment. In this trial of 26 evaluable patients with untreated lymphoma, 9 (35%) patients obtained complete responses and 14 (54%) patients obtained partial responses, for an overall response rate of 88%. As outlined, this represents a doubling of the response rates seen in previously treated patients. Interestingly, of 13 patients with diffuse small lymphocytic lymphoma (5 without plasmacytoid features and 8 with plasmacytoid features), 12 patients (92%) achieved a response. These results are in accordance with those reports of 2-CdA activity in patients with previously untreated Waldenström macroglobulinemia, plasmacytoid lymphocytic lymphoma with marked IgM elevation, in which 22 of 26 patients (85%) achieved a response, including 3 patients who achieved a complete response.17

Although the median number of 2-CdA courses in this study and in the trial of previously treated patients was 3 (range, 1 to 6 courses), the spectrum of hematologic toxicity differed. In untreated patients, significant neutropenia was more frequent than thrombocytopenia, whereas the reverse was true in previously treated patients. During the median of 33 months after the administration of 2-CdA, three patients died with evidence of transformation to higher-grade neoplasms. About one third of patients with low-grade lymphomas evolve into higher-grade histologies over time, and this risk is independent of previous alkylator therapy.15 Fludarabine, a closely related nucleoside drug to 2-CdA with a similar clinical spectrum of activity, administration to patients with chronic lymphocytic leukemia did not show evidence of predisposition to the development of Richter transformation.18

We have previously reported that chronic lymphocytic leukemia patients, treated with 2-CdA at 0.1 mg/kg/d by 7-day continuous infusions or 0.028 mg to 0.14 mg/kg/d by 2-hour infusions on 5 successive days, achieved equivalent response rates and toxicities.19 A confirmatory study has been published.20 Pharmacokinetic studies of 2-CdA administered as a 2-hour bolus have shown a delayed excretory phase, and there is prolonged intracellular retention of 2-chlorodeoxyribonucleotides.21,22 Accordingly, the Cancer and Leukemia Group B (CALGB) is conducting a phase II study of 2-CdA administered as a 0.14 mg/kg 2-hour bolus for 5 days every month in patients with advanced stage, untreated indolent lymphomas. The results of this trial will establish the response rates and toxicities of 2-CdA in larger numbers of patients treated with this new administration schedule in a multi-institutional setting. In an attempt to further improve response rates in patients with alkylator-refractory low-grade lymphomas, studies are presently being conducted at Scripps Clinic with the combination of 2-CdA, which impairs DNA repair, and mitoxantrone, a DNA-damaging agent.

These results establish the major activity of 2-CdA in patients with previously untreated low-grade lymphoma, especially diffuse small lymphocytic histology. The comparative efficacy of 2-CdA with respect to the standard treatments of low-grade lymphoma will require a randomized trial. The identification of new agents and novel therapeutic interventions for the treatment of patients with untreated low-grade lymphomas will expand the existing therapeutic armamentarium so that potentially curative strategies can begin to be developed.

REFERENCES


2-Chlorodeoxyadenosine activity in patients with untreated, indolent non-Hodgkin’s lymphoma

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