Adult T-Cell Leukemia-Lymphoma Successfully Treated with 2-Chlorodeoxyadenosine

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Adult T-cell leukemia-lymphoma (ATL) is resistant to currently available chemotherapy and has a poor prognosis. We describe here a patient with ATL successfully treated with 2-chlorodeoxyadenosine (2-CdA). A 75-year-old Japanese male with an acute type of ATL, who had become resistant to the initial cytotoxic chemotherapy, was treated with 2-CdA administered by continuous drip infusion of 0.09 mg/kg/d for seven consecutive days in one month (one cycle). After three cycles of treatment, partial remission (PR) was achieved. Surprisingly, 249 days after the administration of 2-CdA, ATL cells completely disappeared from the peripheral blood. PR was maintained during 10 weeks until evidence of a new lymphadenopathy. No remarkable toxicity of 2-CdA occurred.

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Key words: purine nucleoside analog, partial remission

Introduction

A purine nucleoside analog, 2-chlorodeoxyadenosine (2-CdA) has been proved to be effective in a variety of lymphoid malignancies, including not only those of B-cell origin but also of T-cell origin (1, 2). However, there are no clinical data available as to whether this agent is also effective against adult T-cell leukemia-lymphoma (ATL), which has a poor prognosis despite various combination chemotherapies (3-5). Here, we report effective treatment with 2-CdA in a patient with ATL, shown in a part of the results of a cooperative phase I study in Japan.

Case Report

A 72-year-old Japanese male was diagnosed as having acute-type ATL in October 1994. The diagnosis was confirmed by positive serum human T-cell leukemia virus type I (HTLV-I) antibodies (x8,192) and by monoclonal integration of the HTLV-I proviral DNA in the peripheral blood mononuclear cells. He was first treated for about eight months with MST-16 [4,4'-(1,2-ethanediyl)bis(1-isobutoxycarbonyloxymethyl-2,6-dioxopiperazine)], an orally administered bis (2,6-dioxopiperazine) analog and an inhibitor of topoisomerase II (6), because a phase II study showed that MST-16 produced a 59% complete remission (CR) and partial remission (PR) in 17 previously untreated patients with ATL in Japan (7). We gave MST-16 orally for five consecutive days every three weeks in the daily dose of 1,600 mg in the first four courses and then 2,400 mg in the subsequent seven courses. After initial seven courses, a minor response was observed. However, he gradually became refractory to this drug. He was hospitalized because of the deterioration of leukocytosis (196.9x10^9/l with 90% ATL cells) and generalized lymphadenopathy (the largest lymph node measured 5.2x2.8 cm in the right axilla) with bone marrow invasion of ATL cells (51.2%). No hepatosplenomegaly was seen. His hemoglobin concentration (13.0 g/dl) and platelet count (230x10^9/l) were normal. The serum lactate dehydrogenase (LDH) and soluble interleukin-2 (IL-2) receptor (sIL-2R) levels were 3,240 IU/l and 8,140 U/ml, respectively. There was no hypercalcemia (9.4 mg/dl).

The patient was eligible for a phase I clinical study of 2-CdA (8) in which 2-CdA was administered as a continuous infusion in a daily dose of 0.09 mg/kg over 7 days, starting on August 8th, 1995, three weeks after the last administration of MST-16. Three courses of 2-CdA were repeated at 28-day intervals. At the completion of the study the response was minimal. However, leukocytosis, lymphadenopathy and bone marrow infiltration of ATL cells continued to be overcome and a maximum response was observed in March 1996 approximately five months after the termination of administration of 2-CdA. ATL cells completely disappeared from the peripheral blood, the
lymphadenopathy was reduced to 4% with the sum of the products (the right axillary lymph node measured 1.0x0.4 cm), serum LDH level returned to normal (281 IU/l), sIL-2R level decreased to 2,150 U/ml. No significant adverse drug reactions occurred. In April 1996, a relapse was noted with the appearance of skin rash and new lymph node swelling in the right inguinal region. The duration of partial remission was 10 weeks (Fig. 1).

**Discussion**

2-CdA is highly effective for B-cell malignancies, especially for hairy cell leukemia (9). It may also be effective for T-cell malignancies, because, in vitro, T cells are more vulnerable than B cells to the action of 2-CdA (10). O'Brien et al (2) treated 22 patients with T-cell malignancies with 2-CdA administered as a continuous infusion in a daily dose of 4 mg/m² over 7 days. Nine patients (41%) responded including four with CR. They concluded that 2-CdA is an effective therapy for some T-cell malignancies and it deserves wider evaluation in this subset of patients. Their results, coupled with the observations that another purine deoxynucleoside analogue, 2'-deoxycoformycin, was an effective agent against ATL (11–13), prompted us to investigate whether 2-CdA showed activity in ATL, a T-cell malignancy caused by HTLV-I (14) and generally resistant to cytotoxic chemotherapy (3–5).

In our patient with an acute type of ATL who had been given 11 courses of MST-16 and had become resistant to this drug, 2-CdA led to a partial response that was apparently biphasic (Fig. 1). The first phase was after the first course of 2-CdA in which a rapid decrease of peripheral blood ATL cells and a shrinkage of lymphadenopathy were observed. After the second course, slight deterioration was noted. A more lasting effect, including a decrease in bone marrow ATL cells, followed the third course, that is the second phase. ATL cells in the peripheral blood completely disappeared eight months after the start of the 2-CdA therapy. Suppression of CD4⁺ lymphocyte counts (decreased ratio of CD4⁺/CD8⁺) persisted, thereafter, until a relapse (Table 1). Interestingly, down-regulation of CD25 on peripheral blood ATL cells was already noted in the first phase (day 28) (Table 1). These findings provide some insight into the mechanism of the action of 2-CdA on ATL because CD25 has an important role in the proliferation of ATL cells (15). No remarkable toxicity of 2-CdA occurred.

![Figure 1](image_url)

**Figure 1.** Clinical course. ¹E erythroid cells; ²G granulocytes; (The area between G and ATL cells represents normal bone marrow cells other than erythroid cells and granulocytes); ³Lymphadenopathy is represented by the sum of the products of all the lymph nodes palpable; ⁴sIL-2R soluble interleukin-2 receptor.
ATL Successfully Treated with 2-CdA

Table 1. Immunophenotyping of Peripheral Blood Mononuclear Cells

<table>
<thead>
<tr>
<th>Antigen</th>
<th>before 2-CdA day-34</th>
<th>after 2-CdA day 28</th>
<th>day 72</th>
<th>day 179</th>
<th>day 249</th>
<th>day 308</th>
<th>day 333</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD2</td>
<td>97.9</td>
<td>97.1</td>
<td>95.7</td>
<td>37.7</td>
<td>49.6</td>
<td>50.4</td>
<td>58.3</td>
</tr>
<tr>
<td>CD3</td>
<td>86.1</td>
<td>84.5</td>
<td>54.3</td>
<td>15.2</td>
<td>18.3</td>
<td>32.1</td>
<td>37.0</td>
</tr>
<tr>
<td>CD4</td>
<td>81.6</td>
<td>95.5</td>
<td>96.9</td>
<td>13.1</td>
<td>8.4</td>
<td>16.5</td>
<td>13.3</td>
</tr>
<tr>
<td>CD5</td>
<td>94.6</td>
<td>96.8</td>
<td>98.8</td>
<td>47.5</td>
<td>41.4</td>
<td>52.2</td>
<td>47.3</td>
</tr>
<tr>
<td>CD7</td>
<td>0.7</td>
<td>1.1</td>
<td>0.6</td>
<td>27.6</td>
<td>48.3</td>
<td>36.0</td>
<td>44.9</td>
</tr>
<tr>
<td>CD8</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
<td>13.2</td>
<td>24.9</td>
<td>24.4</td>
<td>31.2</td>
</tr>
<tr>
<td>CD19</td>
<td>0.6</td>
<td>0.4</td>
<td>0.1</td>
<td>50.3</td>
<td>42.5</td>
<td>40.4</td>
<td>34.1</td>
</tr>
<tr>
<td>CD25</td>
<td>39.4</td>
<td>2.6</td>
<td>3.4</td>
<td>2.6</td>
<td>3.8</td>
<td>8.5</td>
<td>5.8</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>48.4</td>
<td>43.7</td>
<td>40.5</td>
<td>57.5</td>
<td>45.8</td>
<td>58.6</td>
<td>59.1</td>
</tr>
<tr>
<td>WBC/μl</td>
<td>164,000</td>
<td>124,600</td>
<td>86,300</td>
<td>9,500</td>
<td>5,800</td>
<td>6,900</td>
<td>6,300</td>
</tr>
<tr>
<td>(ATL cell)</td>
<td>(98%)</td>
<td>(87%)</td>
<td>(85%)</td>
<td>(27%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
</tr>
</tbody>
</table>

Antigens are listed according to lineage of cell differentiation. Numbers indicate the percentage of the peripheral blood mononuclear cells expressing surface antigens.

Our results suggest that 2-CdA may be an effective agent for patients with ATL and warrants further studies. A multicenter phase II study of 2-CdA is ongoing in Japan.

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References