**2-Chlorodeoxyadenosine Therapy in Patients With T-Cell Lymphoproliferative Disorders**

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Mature T-cell lymphoproliferative disorders comprise a heterogeneous group of diseases for which there is no standard therapy. These disorders are uncommon, and are usually treated similarly to their B-cell counterparts, but with less success. Nucleoside analogues have proven effective in indolent B-cell disorders but have been less well explored in T-cell malignancies. We treated 22 patients with mature T-cell lymphoproliferative diseases with 2-chlorodeoxyadenosine (2-CDA) administered as a continuous infusion at a daily dose of 4 mg/m² over 7 days. Nineteen of the patients had received prior therapy with a median number of prior regimens of three. Eleven patients had leukemia or large granular lymphocytosis, eight patients had mycosis fungoides, and three had T-cell lymphoma. Nine patients (41%) responded to 2-CDA. Four of the patients had responses that were complete remissions, and three of these four patients remain in remission at 23, 24, and 33 months. The only important toxic effects were fever or infection, seen during 38% of courses. In conclusion, 2-CDA appears to be an effective therapy in T-cell lymphoproliferative disorders and deserves wider evaluation in this subset of patients.

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Submitted December 3, 1993; accepted April 5, 1994.

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**Patients and Methods**

**Study Population.** Twenty-two patients were treated after written informed consent was obtained. Criteria for entrance into the study required the patient to have a Zubrod performance status ≤ 3, and normal hepatic and renal functions.

Patient characteristics are outlined in Table 1. The diagnosis varied but all patients had T-cell disorders. Two patients had LGL and one patient had T-PLL. Four patients had cells that were morphologically identical to B-CLL cells, ie, small lymphocytes. All four had greater than 95% T lymphocytes and were characterized as having T-CLL. Three patients had circulating cells with irregular nuclear outlines, nuclear indentations, and serpentine configurations. These were indistinguishable from small Sezary cells and may represent the entity of Sezary cell-like leukemia described by Matutes et al. None of these patients had skin involvement.

Eight patients had MF. One of these patients had stage I disease, one had stage II disease, and the rest had stage III-IV disease. Two patients had peripheral T-cell lymphomas (mixed-cell lymphoma), and one had a T-cell large cell lymphoma (LCL). One patient had severe pancytopenia, a normal bone marrow (BM), and splenomegaly. Splenectomy showed a monomorphic population of small T lymphocytes in the red pulp. Immunoperoxidase staining was positive for CD3 and CD57 and the diagnosis was most consistent with LGL without a leukemic phase. The patient continued to have an absolute granulocyte count of 100 to 200/µL and B symptoms, so chemotherapy was administered.

The median age of the patients was 65 years (range, 34 to 78 years); 10 (45%) were men and 12 were women (55%). Eighty-two percent had a Zubrod performance status ≤ 1. The median time from diagnosis to treatment with 2-CDA was 14 months (range, 0 to 90 months). Nineteen patients (86%) had received therapy before 2-CDA and the median number of prior regimens was three (range, 1 to 6).

Eight of 10 patients (80%) with leukemia had Rai stage III-IV disease. Four leukemic patients had received prior fludarabine therapy. One patient had a transient response but had then progressed with therapy. Three patients had no response to fludarabine after receiving three to five courses. For patients with leukemia, the median hematologic parameters at the start of therapy were white blood cell (WBC) count, 91 × 10³/µL (range, 4.1 to 51 × 10³/µL); hemoglobin level, 10.2 g/dL (range, 9.1 to 13 g/dL); and platelet count, 74 × 10³/µL (range, 6 to 240 × 10³/µL). Phenotypic analysis of the leukemic cells is shown in Table 2. Nine patients with leukemia had rearrangement of the T-cell β gene in BM cells, and one patient had T-cell γ rearrangement only.

**Therapy.** 2-CDA was administered as a continuous infusion at a daily dose of 4 mg/m² over 7 days on an outpatient basis. Courses could be repeated at 28-day intervals and responding patients continued on therapy until maximum response. Six patients (27%) received

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Two courses; three patients (14%), three courses; and three patients, (14%) five to seven courses. Ten patients (45%) received only one course because of progressive disease in six patients and death in four patients.

**Response criteria.** For patients with leukemia or LGL, response criteria were those defined by the National Cancer Institute (NCI) Working Group for CLL. Complete remission (CR) required the following: complete resolution of palpable adenopathy and hepatosplenomegaly; neutrophil count, >5000/μL; platelet count, >100,000/μL; hemoglobin level, >11.0 g/dL; lymphocyte count, >4000/μL; and BM aspirate, ≥30% lymphocytes. Partial remission (PR) required a ≥50% decrease in all node-bearing areas and organ enlargement and a ≥50% improvement from baseline of any abnormal hematologic parameters. BM assessment was not required for PR.

For patients with MF and lymphoma a CR required complete resolution of all disease and PR required a ≥50% decrease in all tumor nodules or node-bearing areas and no new lesions.

### RESULTS

**Response.** All patients were evaluable for response. Nine patients responded to 2-CDA for an overall response rate of 41% (Table 3). Four patients (18%) achieved CR, 1 T-PLL, 1 MF (Fig 1), and 2 LGL. Five patients achieved a PR (23%) (2 T-CLL, 1 Sezary cell leukemia, 1 T-LCL, and 1 peripheral T-cell lymphoma). One of the four patients who had received prior fludarabine therapy responded to 2-CDA. All patients achieving PR and one patient with CR have relapsed at a median of 7 months (range, 5 to 26 months). Three patients achieving CR remain in remission at 30+, 36+, and 54+ months. The median overall survival was 12 months.

One of eight patients with MF responded to 2-CDA. Prior therapy in this patient included steroids, ultraviolet radiation, topical nitrogen mustard, and electron beam therapy. His last treatment before 2-CDA was cis-retinoic acid, to which he failed to respond. Three of the eight patients with MF had failed to respond to systemic chemotherapy. The three patients with lymphoma were all refractory to combination chemotherapy; one achieved a PR with 2-CDA.

Responses were seen in five of the patients (50%) with leukemia. One patient (T-CLL) received no therapy before 2-CDA and he achieved a PR. One patient with LGL received interferon; he achieved a CR with 2-CDA. Fludarabine was the only previous treatment in two patients and neither responded to 2-CDA. The remaining six patients had failed alkylating-agent–based therapy (and fludarabine in two cases) and two achieved a PR with 2-CDA.

Responses according to phenotype were examined in the patients with leukemia. Seven patients had CD4+ T cells, of whom 4 (57%) responded to 2-CDA. There was one response out of two patients with LGL leukemia and CD8 predominance (the patient with LGL diagnosed by splenectomy also responded). The only patient with T-CLL whose lymphocytes were strongly positive for both CD4 and CD8 failed to respond.

**Toxicity.** Seventeen patients began 2-CDA therapy with an absolute neutrophil count >1000/μL. Nadir counts were recorded for 15 of the 17 patients. Five (33%) had a decrease in their neutrophils to <1000/μL, with three (20%) being <500/μL. Fifteen patients began therapy with a platelet count >100 x 10^3/μL and of 13 patients with information on nadir counts, 4 (31%) developed thrombocytopenia <100 x 10^3/μL. A total of 49 courses of 2-CDA was administered.
Sepsis or pneumonia occurred in nine courses (18%). Fever of unknown origin was seen in four courses (8%). Minor infections were noted in six courses (12%).

Three patients developed evidence of cumulative myelotoxicity with 2-CDA. The first patient achieved a PR of her large cell lymphoma after two courses. The platelet count at the start of treatment was 150,000/µL, and decreased to 82,000 after the first course. On day 35 of the second course the platelet count was 35,000/µL. She was not given further therapy; 2 months later the platelet count was 251,000/µL. The second patient had MF and received three courses of 2-CDA. The platelet count before 2-CDA was 184,000/µL and decreased after two courses to 74,000/µL. He had a minor response and 2-CDA was held. By day 110 the platelet count had recovered to 107,000/µL, and he received a third course of 2-CDA for only 4 days, with a subsequent decrease of the platelet count to 59,000/µL; because he had no further response he did not receive more 2-CDA. The third patient had LGL diagnosed on splenectomy. He received three courses of 2-CDA. The platelet count before 2-CDA was 209,000/µL and after 2 courses was reduced to 93,000/µL. He received a third course of 2-CDA at full dose and had a platelet nadir of 37,000/µL on day 66. The patient was otherwise in complete remission. He had a slow rise in the platelet count, which finally increased above 100,000/µL 19 months after the third course of 2-CDA. He continues in complete remission 54 months from the initiation of treatment.

Four patients died during the first course of 2-CDA. Two patients with leukemia died of disseminated Candida infection. Both had received prior fludarabine. The only patient with a Zubrod performance status of 3 died on day 16 of the treatment. The cause of death was uncertain but likely related to progressive disease. One patient with lymphoma died at 4 weeks with progressive disease.

Nonhematologic toxicity was minimal with 2-CDA. One patient had nausea and vomiting with both courses of 2-CDA. One patient complained of increasing fatigue. One patient noted numbness in the feet.

DISCUSSION

T-cell leukemias and lymphomas are an uncommon and heterogeneous group of disorders for which there is no standard therapy. Although some patients with LGL may have an indolent progression of disease and not require therapy for some time, most patients with the other disorders will necessitate initial therapy. Patients with T-CLL or T-PLL usually have high WBC counts, markedly enlarged spleens, anemia, and thrombocytopenia. They are generally treated with the same regimens used for B-CLL, including alkylating agents such as chlorambucil or cyclophosphamide, in combination with prednisone. Because of the rarity of these disorders, there have been few disease-specific clinical trials. However, the experience reported with T-cell leukemias suggests that the response rate to standard agents is significantly inferior to that with B-CLL.1,4

Recently, nucleoside analogues have shown activity in a variety of indolent lymphoproliferative disorders. DCF was effective in both B- and T-cell disorders. Smyth et al reported a 60% response rate in T-cell acute lymphocytic leukemia and three responses in six patients with MF using a DCF dose of 10 mg/m² daily for 5 days. At this dose significant central nervous system and renal toxicities were seen. A lower dose of 4 mg/m² weekly has been used in indolent disorders. Using this dose schedule, Dearden et al treated 19 patients with T-cell disorders including T-PLL, T-CLL, Sezary syndrome, and lymphoma, and observed seven responses (37%), all in patients with CD4+, CD8- markers.5 Matutes et al31 treated 31 patients with T-PLL with the same dose schedule of DCF and noted 15 responses (48%). The response rate in patients with a CD4+, CD8- phenotype was 58%, versus 27% in patients with CD8 (±CD4) positivity. All responses, including three CR, were short-lived.21

Fludarabine is an effective agent in B-CLL with response rates ranging from 57% to 85%, depending on the use of prior therapy.13,15 We have treated six patients with chronic T-cell leukemias with fludarabine at 30 mg/m² daily for 5 days. One patient had a response after three courses but relapsed after the fifth course (unpublished data).

2-CDA is also effective in B-CLL, with a response rate of 44% in previously treated patients, and an even higher response rate of 89% to 100% in HCL.16,17,22 Saven et al23 treated 15 evaluable patients with cutaneous involvement by T-cell lymphoma with 2-CDA, and observed responses in three of eight patients (38%) with mycosis fungoides, and in four of seven patients (57%) with nonsquamous fungoides histology. One patient in the latter group had a tumor that showed strong CD8 expression. This patient achieved a partial remission.23 Our data using 2-CDA in 22 patients with T-cell lymphoproliferative disorders show a 41% response rate, with several of those responses occurring in heavily pretreated patients. Interestingly, one of the four responses among the T-cell leukemias was in a patient who had received five courses of fludarabine without a response. This patient had an extremely high WBC count at the time of 2-CDA therapy (540 × 10³/µL), and massive hepatosplenomegaly; she achieved a PR with 2-CDA therapy. Unlike the patients treated with DCF and reported by Dearden et al, we saw responses to 2-CDA in patients with either CD4+ or CD8- disease. Our experience, combined with the experience of Saven et al, suggests that 2-CDA may be the best nucleoside analogue therapy for CD8 disease. The drug is well tolerated, with the most common side effect being myelosuppression and infection, effects similar to those seen in patients with B-CLL treated with 2-CDA.

There were two treatment-related deaths, both occurring in leukemic patients who had received fludarabine (and failed to respond) just before treatment with 2-CDA. Both patients had a Zubrod performance status of 1 but neither had any circulating granulocytes at the start of therapy. Both patients died with disseminated fungal infections. This result is similar to our experience in B-CLL using 2-CDA after fludarabine failure, where frequent and severe infections were common.24 Cumulative immunosuppression with the use of tandem nucleoside analogues may be a predisposing factor.

In conclusion, 2-CDA appears to be an effective therapy
Fig 1. Response to 2-CDA in a patient with mycosis fungoides. Skin lesions before treatment (A, B) and after therapy with 2-CDA (C, D).
Fig 1. (Cont'd)
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