Treatment of Hairy Cell Leukemia With 2-Chlorodeoxyadenosine (2-CdA)


We administered one course of 2-chlorodeoxyadenosine (2CdA) at 4 mg/m² daily for 7 days by continuous intravenous infusion to 46 patients with hairy cell leukemia. Complete remissions occurred in 36 patients (78%; 95% confidence limits, 63% to 89%), partial remissions in five (11%), and a minor response in one. One patient died of candida sepsis 3 weeks after beginning treatment and three patients were clearly resistant to therapy. These three either had morphologically atypical hairy cells, less than 20% of which expressed Ig light chain on the cell surface, or had failed prior treatment with deoxycytosine and interferon-α. At a median of 37 weeks since discontinuation of therapy, recurrent thrombocytopenia has developed in one patient, whose marrow remains normal, while a bone marrow relapse has occurred in another patient, whose blood counts remain normal. Treatment produced a greater than 50% decrease in neutrophil count in 26 patients, which lasted 3 to 4 weeks and was associated with an increased incidence of febrile episodes. These episodes occurred in 21 patients but were associated with documented infection in only four patients. Decreases in the number of CD4+ lymphocytes appeared to occur regularly after treatment and have persisted for a median of 18 weeks without obvious clinical significance. Although years of follow-up will be needed, our results confirm Piro et al’s observation (N Engl J Med 322:1117, 1990) that 2CdA appears to be highly effective in the treatment of hairy cell leukemia.

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During the early 1980s, interferons (IFNs; first partially purified, later recombinant) and deoxycytosine and interferon-α (DCF) were introduced as alternatives to splenectomy for the treatment of hairy cell leukemia (HCL). Both IFNs and DCF regularly correct the cytopenias associated with this illness and, unlike splenectomy, both also reduce the number of hairy cells in the bone marrow (BM), although, on average, reduction is more complete and long-lasting after the use of DCF. More recently, Piro et al. reported that another agent, 2-chlorodeoxyadenosine (2CdA), administered as a single 7-day infusion produced complete remissions (CRs) in 11 of 12 patients with HCL, that the twelfth patient obtained a partial remission (PR), that there had been no recurrence of disease in any patient at a median follow-up of over a year, and that, as fibrin clot from fever without apparent infection, the treatment was without toxicity. Unlike DCF, 2CdA is not an inhibitor of adenosine deaminase but rather is phosphorylated by deoxycytidine kinase, accumulating as chlorodeoxyadenosine triphosphate (chlorodATP) in cells rich in this enzyme and poor in deoxynucleotidases. ChlorodATP inhibits enzymes (DNA polymerase, DNA ligase, ribonucleotide reductase) important in DNA repair, thus leading to the accumulation of DNA strand breaks that, in turn, may accelerate the process of “programmed cell death.” Because they target different enzymes with different intracellular distributions, the spectra of activity and/or toxicity of DCF and 2CdA might differ, although both drugs lead to intracellular accumulation of deoxycytidine nucleotides. Piro et al’s report prompted us to undertake a larger trial of 2CdA in HCL. We report here the results in 46 patients.

Patients and Methods

Eligibility criteria were: (1) a morphologic diagnosis of HCL established after examination of marrow aspirate and/or biopsy; (2) either cytopenia (hemoglobin [Hb] < 12 g/dL, neutrophil count < 1.5 × 10⁹/μL, or platelet count < 100 × 10⁹/μL), or extramedullary evidence of HCL; (3) Zubrod performance status of 0 or 1; (4) serum bilirubin less than 2.0 mg/dL, serum creatinine less than 2.0 mg/dL; and (5) provision of informed consent in accordance with the guidelines of our Institutional Review Board, which had previously approved the study. Patients could either be untreated or have received and failed, or been intolerant of, previous therapy. No specific symptoms were required for entry. The diagnosis was confirmed (except in one atypical case described below) by tartrate-resistant acid phosphatase (TRAP) stain. 2CdA, supplied by the Scripps Clinic and Research Foundation (La Jolla, CA), was administered over 7 days by continuous intravenous (IV) infusion at a daily dose of 4 mg/m². Using the usual conversion factor of 40, this dose is, on average, equivalent to the daily dose of 0.1 mg/kg (also administered for 7 days by continuous IV infusion) used by Piro et al. All patients received only a single course of therapy. Treatment was administered on an outpatient basis, and, after observation for a week after completion of treatment, patients were advised that they could return to their homes, which were often at considerable distance from Houston, and obtain weekly blood counts. Patients returned for repeat testing 8 to 16 weeks after the initiation of therapy. This interval, in general, corresponded to that used by Piro et al for initial reevaluation of their patients. Afterward, patients were followed-up off therapy, returning to Houston approximately every 3 to 6 months for follow-up. Pretreatment and posttreatment BM aspirates and biopsies were reviewed by one of the investigators (S.S.). The TRAP stain was routinely performed to aid in morphologic interpretation posttherapy.

The median age of the patients was 51 years. Twenty-seven had received no prior therapy, one had received no therapy aside from splenectomy, and 18 had received IFN, including three who had also received DCF and eight who had also undergone splenectomy. A total of 51 patients had received at least one prior therapy. All of the IFN-treated patients had persistent or recurrent anemia (Hb < 12 g/dL), neutrophilia (neutrophil count < 1.5 × 10⁹/μL), or thrombocytopenia (platelet count < 100 × 10⁹/μL). The median duration of therapy with IFN was 21 months, and a median of 10 months had elapsed between discontinuation of IFN and
initiation of 2CdA. The three patients who had received DCF last received this drug 3, 4, and 26 months before beginning 2CdA; two had persistent cytopenias, with cytopenia as defined above, while one had a normal blood count but persistent hairy cells in the BM. Forty-four of the 46 patients (96%) had either anemia, neutropenia, or thrombocytopenia (defined above) before receiving 2CdA, and 30% had splenomegaly on physical exam. Two patients had no cytopenias before treatment; one had symptomatic splenomegaly and the other mediastinal adenopathy thought to be due to hairy cell infiltration. The median pretreatment neutrophil count was $0.8 \times 10^{9}/\mu L$, the median platelet count was $89 \times 10^{9}/\mu L$, and the median Hb was 11.9 g/dL. In 42 patients, the pretreatment cytopenias before treatment; one had symptomatic splenomegaly and the other mediastinal adenopathy thought to be due to hairy cell infiltration. The median pretreatment neutrophil count was $0.8 \times 10^{9}/\mu L$, the median platelet count was $89 \times 10^{9}/\mu L$, and the median Hb was 11.9 g/dL. In 42 patients, the pretreatment diagnosis of HCL could be made using the BM aspirate (median percentage of hairy cells, 22%); 39 of these 42 also underwent marrow biopsy, which was positive in 33, negative in three, and inadequate in three. In four patients in whom the pretreatment marrow aspirate was inadequate, the diagnosis was based on the biopsy. All of the patients were free of fever or infection immediately before therapy.

Response criteria after treatment were as follows: (1) CR—the absence of hairy cells in the BM or the presence of less than 1% atypical cells that, however, could not be definitely called hairy cells, together with the disappearance of all evidence of HCL on physical exam, and a platelet count greater than 100,000/μL, a neutrophil count greater than 1,500/μL, and an Hb of ≥12 g/dL; (2) PR—the marrow contained 1% to 5% hairy cells, there was at least a 50% reduction in palpable evidence of HCL, and the blood counts were as defined for CR; (3) minor response (MR)—the marrow and physical findings were as described for CR or PR, and there was correction of greater than one cytopenia, as described above without worsening of any other blood count; (4) failure—other responses.

RESULTS

CRs were observed in 36 patients (78%), PRs in five (11%), an MR in one (2%), and four patients (9%) failed to respond. Among the 36 patients classified as CR, 13 had pancytopenia at the start of treatment, 12 had two cytopenias, and 11 had either isolated neutopenia, or thrombocytopenia (three patients), or anemia (one patient). Of the five patients considered as PR, one began treatment pancytopenic, two had two cytopenias, one had isolated neutropenia, and one had isolated thrombocytopenia. The median time to CR was 10 weeks (range, 4 to 42 weeks) and the median time to PR was 15 weeks (range, 10 to 26 weeks). The patient considered to have had a MR began treatment with 66% hairy cells in the marrow, a platelet count of 91,000/μL and an Hb of 8.9 g/dL. Eighteen weeks after treatment, the marrow contained less than 1% atypical cells and the platelet count had increased to 226,000/μL, but the Hb was only 9.3 g/dL.

The four patients who failed to improve included one who died of candida sepsis 3 weeks after treatment began (early death) and three who were considered resistant to therapy. The patient who died of candidiasis was a 57-year-old man who was our only patient with a documented history of alcoholism, and was also our only patient who had been receiving corticosteroids (prednisone 20 mg daily for 2 months) at the time of initiation of 2CdA, at which time the neutrophil count was 200/μL. Prednisone was discontinued on the day 2CdA began. The patient was admitted to hospital with fever on day 3 of treatment, developed acute tubular necrosis thought secondary to sepsis on day 10, and, despite dialysis and administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) beginning at that time, died on day 20 with a neutrophil count less than 100/μL. Blood cultures were negative until the last week of life, when candida tropicalis was grown.

Table 1 gives the characteristics of the three patients considered resistant to 2CdA. Follow-up time after start of 2CdA ranged from 20 to 33 weeks, which was longer than the time needed to see the beginnings of a response in any of the 42 patients considered to have a CR, PR, or MR. Characteristics distinguishing resistant from responding (CR, PR, or MR) patients included atypical pretreatment morphology: the resistant patients UPN 1 and UPN 2 were the only two patients of the 46 treated who had variant morphology, and UPN 1 was the only one who was TRAP negative. Additionally, although both UPN 1 and UPN 2 had coexpression of surface antigens CD11c, CD20, and CD22 on greater than 90% of their hairy cells (the pattern typical of HCL25), in both patients Ig light chain was only weakly expressed on the hairy cell surface (<20% of the hairy cells positive), with expression of these markers determined by flow cytometric analysis.26 In contrast, among 32 patients who had either a CR, PR, or MR and in whom surface light chain expression was analyzed, only three had...
less than 20% hairy cells expressing surface-light chain before therapy ($P = .05$, Fisher exact test for the comparison between the proportion of responding and nonresponding patients with < 20% hairy cells positive for surface light chain expression before therapy). Finally, UPN 1 and UPN 3 were the only two patients who began treatment with normal blood counts and UPN 2 and UPN 3 were two of the only three patients who had received and proven resistant to DCF (the third such patient achieved a PR after 2CdA, but has had a BM relapse; see below).

Median pretreatment and posttreatment counts (in all 46 patients) were 89 and $200 \times 10^3/\mu$L (platelets), 0.8 and $3.1 \times 10^3/\mu$L (neutrophils), and 11.9 and 14.2 g/dL (Hb). Of 28 patients who began treatment with a platelet count less than $100 \times 10^3/\mu$L, the count was observed to increase above this level in 26 (Fig 1A) a median of 8 weeks (range, 3 to 17 weeks) after the initiation of treatment, while 36 of the 38 who had a pretreatment neutrophil count less than $1.5 \times 10^3/\mu$L and 22 of the 25 with a pretreatment Hb less than 12 g/dL had increases above these levels (Fig 1B and C) observed a median of 10 weeks (range, 4 to 26 weeks) and 12 weeks (range, 7 to 42 weeks), respectively, after beginning therapy. When patients who began treatment with two or three cytopenias were seen at first follow-up, the cytopenias were usually observed to have been corrected simultaneously; in instances in which this was not the case, the platelet count was usually the first to be corrected. Thus, in patients in whom treatment corrected both the platelet and neutrophil counts, correction appeared simultaneous in 17 and the platelet count was corrected first in four, while when both platelets and Hb were corrected, correction appeared simultaneous in eight and platelets were corrected first in six.

Follow-up in responding patients. The median time since response in the 42 responding patients (36 patients CR, five patients PR, one patient MR) is currently 37 weeks (34 weeks in the CR group and 40 weeks in the PR group). Recurrent thrombocytopenia has occurred in one patient

![Fig 1. Pretreatment and posttreatment 2CdA platelet count (A), neutrophil count (B), and Hb (C) in all 46 patients. Each patient is represented by a pretreatment bar and a posttreatment bar.](image-url)
who began treatment with a platelet count of 19,000 that increased to 106,000 after a CR and is currently 82,000 after a CR and is currently 82,000 4 months after CR was observed. The patient’s marrow aspirate and biopsy continue without evidence of HCL. However, a second patient has had a clear relapse in the BM.

**Toxicity.** The neutrophil count temporarily decreased by at least 50% in 26 patients (57%), with the decrease occurring in the first 1 to 2 weeks after beginning therapy and generally reversing by the end of week 4. Febrile episodes occurred in 21 patients (46%), of whom two had pneumonia, one phlebitis, one at the site of catheter insertion, one fatal candida sepsis, and 17 no documented infection. In neither case of pneumonia was an etiologic organism identified. Episodes of fever and infection were limited to the first month after beginning therapy (with the exception of UPN 3 who, as noted above, had no response to treatment) and occurred in 15 of the 26 patients in whom the neutrophil count decreased by ≥50% during treatment but in only 6 of the 20 in whom the count did not decrease or decreased less than 50%. A moderately severe rash occurred in one patient. There was no other symptomatic toxicity. However, decreases in the number of lymphocytes expressing the CD4 surface antigen (“helper” phenotype) occurred in all 15 patients in whom these cells were enumerated before and after treatment, and decreases in the number of CD8 surface antigen “positive” lymphocytes (“suppressor” phenotype) occurred in 12 of these 15. Each of the 15 belonged to the group of 42 responding patients. As seen in Table 2, the decreases in CD4+ and CD8+ lymphocytes was dramatic at times. The median pretreatment and posttreatment CD4 counts were 588 and 126/µL, respectively, and the CD4 count decreased below 50/µL in two patients. Corresponding medians for CD8 counts were 266 and 100/µL. The CD4 count remained decreased at 8 weeks after initiation of therapy.

<table>
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<th>Patient No.</th>
<th>Pretreatment CD4/CD8 Count (per µL)</th>
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<th>17-25 Weeks*</th>
<th>26-34 Weeks*</th>
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*Weeks after initiation of therapy.

**DISCUSSION**

Our results in 46 patients confirm Piro et al’s initial observation, made in 12 patients, that 2CdA appears highly effective in the treatment of HCL. Using our criteria, we observed a CR rate of 78% (95% confidence limits, 63% to 89%) and a CR + PR rate of 89% (95% confidence limits, 77% to 96%). Table 3 places the CR and CR + PR rates observed in this study within the context of other investigators’ criteria for response in HCL. As seen, our CR rate and CR + PR rate would be the same using our criteria or those developed by Cassileth et al17 or Kraut et al18 for DCF, and our CR + PR rate would also be the same using our criteria or those used by the University of Chicago group for IFN studies.19 With the criteria used by Piro et al9 for their study of 2CdA (which requires a platelet count >130,000/µL, rather than 100,000/µL, for CR) our CR rate would be 76% and the 95% confidence limits about this rate (61% to 88%) would overlap the 95% confidence limits about the CR rate reported by Piro et al (11 of 12; 95% confidence limits, 61% to 100%). Similarly, the 95% confidence limits about our CR + PR rate of 89% (77% to 96%) overlap the 95% confidence limits about the CR + PR rate reported by Piro et al (12 of 12; 74% to 100%). In short, our data confirm Piro et al’s observations of a high response rate after therapy of 2CdA with DCF.

However, the relatively large numbers of patients we treated have permitted certain new observations to be made. First, it seems clear that, at a minimum, BM relapse may occur after cessation of treatment. As noted, the one such relapse observed by date occurred in that patient who has been follow-up the longest (71 weeks), although it should be pointed out that this patient was unusual in being resistant to 4 months of DCF at 4 mg/m2 every other week. However, given that the patient with the longest follow-up has had a relapse, it must be stressed that median follow-up in our patients is only 37 weeks, whereas follow-up in DCF- or IFN-α–treated patients is measured in years.20,21 Clearly, comparison of recurrence rates in large numbers of patients treated with 2CdA, DCF, or IFN-α will require longer follow-up.

Additionally, although we, like Piro et al,7 did not note...
toxicities such as nausea/vomiting, diarrhea, or lethargy, which have been reported to occur, although infrequently, after use of even low-dose DCF\textsuperscript{8,21,22} (4 mg/m\textsuperscript{2} every other week), our results indicate that fever or infection can occur in the few weeks after treatment with 2CdA. Like DCF, 2CdA is associated with a small but definite risk of fatal infection during this period, which corresponds to the time of maximum drug-induced neutropenia, although it should be pointed out that the one fatal infection that we observed occurred in a patient who had received corticosteroids for the 2 months before beginning 2CdA, and who thus may have been predisposed to the fungal infection that caused his death.

Of particular note, our report makes it clear that 2CdA, like DCF,\textsuperscript{2,24} can produce profound depression in the number of CD4\textsuperscript{+} lymphocytes. Carrera et al\textsuperscript{23} recently reported that within 6 months of completing 2CdA, CD4/CD8 ratios had reverted to normal in most patients, although our experience suggests that low numbers of CD4\textsuperscript{+} lymphocytes may persist longer than this; little is known about the functional capabilities of the remaining CD4\textsuperscript{+} cells. With neither DCF nor 2CdA do there yet appear to be any major clinical consequences of the "immunosuppression."\textsuperscript{21,22} Indeed, depression in the number of CD4\textsuperscript{+} or CD8\textsuperscript{+} lymphocytes may be relevant to the mechanism of action of these drugs were these lymphocytes to produce cytokines that support the presence of hairy cells. As with comparison of recurrence rates, only further observation will indicate whether depression of CD4 lymphocyte number lasts longer with DCF or with 2CdA, or if clinical consequences of the immunosuppression eventually develop. Similar time (and patient accrual) will be needed to determine if patients who are resistant to DCF will be resistant to 2CdA (as suggested by data in Table 1), if patients who are relatively unlikely to respond to 2CdA can be identified (variant morphology, negative TRAP stain, or absence of surface light chain expression, also as suggested by data in Table 1), or if after relapse responses can be reinduced with a second course of 2CdA (as is the case with IFN-\alpha\textsuperscript{10} or DCF\textsuperscript{17,18}). Although several years will thus be probably required to define the role of 2CdA in the treatment of HCL, 2CdA, like IFN-\alpha or DCF, does appear to be a highly effective agent in this disease.

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Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA)

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