Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience

Punit Chadha, Alfred W. Rademaker, Prateek Mendiratta, Benjamin Kim, Darren M. Evanchuk, David Hakimian, LoAnn C. Peterson, and Martin S. Tallman

2-chlorodeoxyadenosine (2-CdA), a purine analog, has become universally accepted as the agent of choice in treating hairy cell leukemia (HCL). However, few studies have reported long-term outcomes after 2-CdA treatment. Between January 1990 and June 2003, 86 consecutive patients with HCL were treated with a single 7-day course of 2-CdA by continuous infusion at a dose of 0.1 mg/kg per day. Of the 86 patients (mean age: 49 years), 67 patients (79%) achieved a complete remission (CR); 18 patients (21%) achieved a partial remission (PR); and 1 patient’s response was unable to be assessed. The progression-free survival (PFS) for initial relapse after 12 years was 54%. At a median follow-up of 9.7 years (range, 0.3-13.8 years), 31 (36%) of 85 patients relapsed. There were 23 relapsed patients treated with a second cycle of 2-CdA; 2 patients were treated with alternative agents; and 6 patients were observed. Of the 23 relapsed patients retreated with 2-CdA, 12 (52%) achieved a CR and 7 (30%) patients achieved a PR (overall response rate: 83%). The overall survival (OS) rate after 12 years was 87%. There were 15 patients (17%) who developed other malignancies. Long-term follow-up of up to 14 years (median: 9.7 years) showed an excellent PFS and OS for HCL patients after 2-CdA treatment.

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Introduction

Hairy cell leukemia (HCL) is a chronic lymphoproliferative disorder characterized by varying degrees of cytopenias and the presence of a malignant clone of B cells with irregular cytoplasmic projections. Although HCL generally has an indolent course, the majority of patients require treatment for cytopenias or symptomatic splenomegaly. Treatment options have evolved over the past 20 years and now include the purine analogs 2-chlorodeoxyadenosine (2-CdA) and 2′-deoxycoformycin. Initial studies demonstrate that treatment with 2-CdA leads to complete remissions (CRs) in the majority of patients with minimal toxicities. Few studies have reported long-term outcomes of patients with HCL treated with 2-CdA. The 4-year follow-up data have previously been reported. However, given the indolent natural history of the disease, long-term follow-up of patients with HCL treated with 2-CdA is important.

Patients, materials, and methods

Patient population

Between January 1990 and June 2003, 86 consecutive patients with HCL were treated at the Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Patients were followed for a median follow-up of 9.7 years (range, 0.3-13.8 years). Diagnosis was established by morphologic review of the peripheral blood smear and bone marrow aspirate and biopsy. In each case, an immunophenotypic characteristic of HCL was demonstrated by flow cytometry, or the neoplastic cells were documented to be B lineage by immunohistochemistry and tartrate-resistant acid phosphatase (TRAP) positive by cytochemical stains. Pathology slides were reviewed by a single hematopathologist (L.C.P.). Characteristics of the patients are listed in Table 1. Of the 86 patients, 60 were previously untreated. A total of 26 patients were previously treated with the following therapies: 7 had undergone splenectomy, 11 were treated with interferon (IFN) only, 4 had undergone splenectomy followed by IFN, 2 had undergone splenectomy followed by IFN and 2′-deoxycoformycin (2′-DCF), 1 was treated with IFN followed by 2′-DCF, and 1 patient was treated with only 2′-DCF. Some follow-up complete blood counts (CBCs), bone marrow aspirates, and core biopsies were obtained from referring institutions until August 2004 under the approval of the institutional review board of Northwestern University.

Eligibility

Eligibility criteria for treatment with 2-CdA included the following: (1) pathologically confirmed diagnosis of HCL based on bone marrow aspirate, core biopsy, and peripheral blood smear obtained within 2 weeks of study entry; (2) evidence of active disease including any of the following—neutropenia (absolute neutrophil count [ANC] < 1.5 × 109/L [1500/µL]), anemia (hemoglobin [Hgb] level < 120 g/L [12 g/dL]), thrombocytopenia (platelet [Pt] count < 100 × 109/L [100,000/µL]), or symptomatic splenomegaly or adenopathy; (3) no evidence of active infection; (4) no prior treatment within 4 weeks of receiving 2-CdA; and (5) normal renal and hepatic function.

Administration of 2-CdA

All patients received a single cycle of 2-CdA at a dose of 0.1 mg/kg per day by continuous intravenous infusion for 7 days. Until the drug became
Table 1. Characteristics of 86 patients with HCL

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, y, median (range)</th>
<th>WBC, × 10⁹/L, median (range)</th>
<th>ANC/µL, median (range)</th>
<th>Hgb level, g/dL, median (range)</th>
<th>Pit count, × 10⁹/L, median (range)</th>
<th>Follow-up, y, median (range)</th>
<th>Sex, n (%)</th>
<th>Prior treatment, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Yes</td>
</tr>
<tr>
<td>49</td>
<td>(25-86)</td>
<td>2.5 (0.8-98.3)</td>
<td>816 (10-16 022)</td>
<td>11.2 (5.9-14.7)</td>
<td>79 (11-466)</td>
<td>9.7 (0.3-13.8)</td>
<td>74 (86)</td>
<td>26 (30)</td>
</tr>
</tbody>
</table>

WBC indicates white blood cell count; ANC, absolute neutrophil count; Hgb, hemoglobin; and Plt, platelet.

commercially available in February 1993, 2-CdA was provided by the R. W.

Johnsson Pharmaceutical Research Institute (Raritan, NJ), and patients were

treated on an institutional phase-2 protocol after informed consent per the

Declaration of Helsinki was obtained according to procedures approved by

the institutional review board of Northwestern University. The first 43

patients received 2-CdA as study participants, while the subsequent 43

patients were treated with the commercial drug under the same protocol. In

the majority of cases, patients received 2-CdA on an outpatient basis using

the computerized ambulatory drug delivery (CADD) portable infusion

dump (Pharmacia Deltec, Saint Paul, MN).

Supportive care

At the beginning of the study, all patients who developed neutropenic fevers

were hospitalized, cultured, and given broad-spectrum antibiotics. All

blood cultures remained sterile without evidence of infection. Subsequent

patients who developed neutropenic fevers were evaluated with collection

of blood and urine cultures and treated with an oral antibiotic (usually
ciprofloxacin or levofloxacin). Patients with sterile blood cultures after 48

hours also received a nonsteroidal anti-inflammatory agent. Replacement

blood products were administered for symptomatic anemia or plt counts

less than 15 000/µL. Growth factor was administered only to 2 patients who

presented with life-threatening infections (1 with Legionella pneumonia and 1

with a symptomatic inguinal furuncle).

Initial evaluation and serial studies

Prior to treatment, all patients had a complete history and physical

examination; CBC; hepatic and renal panel; computed tomographic (CT)

scans of the chest, abdomen, and pelvis to assess for splenomegaly and

adenopathy; and unilateral bone marrow aspirate and core biopsy with flow

cytometric immunophenotyping or immunohistochemistry and TRAP. The

initial 43 patients registered to the phase-2 protocol were routinely followed

with CT scans. After data from the first 43 patients were collected and

evaluated, it was determined that obtaining routine CT scans was not

essential in monitoring for relapse in patients after treatment with 2-CdA, and

this practice was subsequently discontinued. During the 7-day treat-

ment course, all patients had daily CBCs with liver and renal function

panels collected on days 1 and 4. CBCs were repeated weekly for 8 weeks,

and liver and renal panels were collected monthly for 3 months. Patients

were also initially treated with allopurinol to prevent tumor lysis syndrome,

but this practice was discontinued after it was discovered that tumor lysis

was rarely observed.

Patients were evaluated for treatment response at 3 months with a

unilateral bone marrow aspirate and biopsy. The decision to assess patients

at 3 months after treatment in the phase-2 protocol was based on the

timeframe for disease assessment used in the initial trials with 2-CdA. The

initial 43 patients registered to the phase-2 protocol were offered a second

cycle of 2-CdA (same dose and duration) after 3-month evaluation if a

partial remission (PR) or no remission (NR) was obtained. After it was

observed that the vast majority of the patients who achieved a PR after the

first cycle maintained stable peripheral blood counts, subsequent patients

were re-treated with a second cycle of 2-CdA (same dose and duration) only

at time of relapse. Patients who had 2 or more relapses were treated with

other agents including rituximab, BL22 immunotoxin, and 2′-DCF. Long-
term follow-up consisted of review of yearly CBCs collected at our

institution or referring institutions. Bone marrow aspirates and biopsy

results were obtained yearly at first and then only when indicated, for

example, if patients had peripheral cytopenias. There were no studies

performed on these patients to analyze immunologic profile (T-cell and

humoral immunity).

Response criteria

At 3-month evaluation following treatment, a CR was defined as exhibiting

all of the following: (1) complete absence of hairy cells in the peripheral

blood and bone marrow; (2) normalization of peripheral-blood counts (Hgb

level > 120 g/L [12 g/dL], white blood-cell count [WBC] ≥ 3000/µL,

ANC ≥ 1.5 × 10⁹/µL [1500/µL], and Plt count ≥ 100 × 10⁹/L [100 000/µL]);

(3) absence of all palpable adenopathy and hepatosplenomegaly; (4)

absence of constitutional symptoms; and (5) disappearance of all abnormal

adenopathy and hepatosplenomegaly. Patients without morphologic evi-
dence of hairy cells, but evidence of minimal residual disease by immuno-
histochemistry of bone marrow core biopsies, as previously defined,4 were

included in the CR group. Patients with mild residual splenomegaly (> 12

buts ≤ 14 cm in craniocaudal dimension) or minimal soft-tissue abnormality

(< 2 cm in diameter) were also considered in CR.

A PR required all of the following: (1) reduction of more than 50% of

hairy cells in the bone marrow core biopsy specimen; (2) increase of

abnormally low peripheral blood counts by more than 50%; and (3)

reduction of abnormal adenopathy or hepatosplenomegaly by more than 50%.

Patients who did not fulfill the criteria for CR or PR were classified as

achieving NR.

Relapse was defined as having any of the following: (1) reappearance

of hairy cells in the bone marrow core biopsy specimen after achieving CR;
(2) reappearance of hairy cells in the bone marrow of patients achieving PR

who had residual splenomegaly only; or (3) increase of residual hairy cells

in bone marrow core biopsy specimens by more than 50%.

Statistical analysis

Progression-free survival (PFS) was measured from the date of first

treatment until relapse date or death from any cause. Observations of PFS

were censored at the date of last contact for patients with no known report of

relapse who were last known to be alive. Overall survival (OS) was

measured from the first day of treatment until death from any cause. PFS

and OS were estimated by the method of Kaplan and Meier.9 Curves were

compared using the log-rank test.

Results

Accrual

There were 86 patients initially treated with a single cycle of

2-CdA. All patients were monitored for toxicities. Of the 86

patients, 85 were assessed for response; 1 patient did not undergo

bone marrow biopsy evaluation at 3 months. Results were analyzed as

of September 1, 2004. Of the original 86 patients, 80 had a recent

CBC collected as of January 2003. Patient characteristics, includ-
ing age (median: 49 years, range, 25-86 years), sex (86% male, 14%
female), and prior treatment (30% yes, 70% no) as well as the

median and ranges of patients’ WBC, ANC, Hgb level, and Plt

counts at time of 2-CdA treatment initiation are listed in Table 1.

Response

Of the 85 assessable patients, 67 (79%) achieved a CR and 18
(21%) patients achieved a PR, for an overall response rate of 100%
(Figure 1). Of the 18 patients achieving a PR, 11 had residual disease in the bone marrow, and 7 had no disease in the bone marrow but had either residual splenomegaly measuring more than 14 cm in craniocaudal length by CT scan (4 patients) or residual internal adenopathy (3 patients). Of the 18 patients who achieved a PR, 6 were re-treated with a second cycle of 2-CdA after the initial 3-month assessment. At 3-month evaluation after cycle no. 2, 3 of these patients achieved a CR and the remaining 3 remained in PR. Of the 18 patients who initially achieved a PR, 5 were re-treated with a second cycle of 2-CdA at time of progression of disease. Of the 18 patients who initially achieved a PR, 6 were simply observed with normal peripheral blood counts. The remaining patient who achieved an initial PR was treated with 2'-DCF and achieved a CR.

The one patient who was not assessed at 3 months after initial treatment for HCL with 2-CdA refused to undergo a bone marrow biopsy but achieved normal peripheral blood counts. He subsequently developed prostate cancer 24 months after 2-CdA treatment and died of complications from metastatic prostate cancer.

Relapse and re-treatment with 2-CdA

At a median follow-up of 9.7 years (range, 0.3-13.8 years), 31 patients (36%) have relapsed from either CR (21 patients) or PR (10 patients) after the initial treatment with 2-CdA (Figure 1). The median time to first relapse for those patients who initially achieved a CR was 35 months, and 10.5 months for those who initially achieved a PR. There was no statistical significance to the median time to first relapse in those who initially achieved a CR versus PR (P = .54 by log-rank).

Of these relapsed patients, 13 were previously treated and 18 were not. Of the previously treated patients who relapsed, 6 were treated with IFN only; 3, with splenectomy alone; 2, with splenectomy followed by IFN and then 2'-DCF; 1, with IFN followed by 2'-DCF; and 1, with 2'-DCF alone. The median time to first relapse for the 18 relapsed patients without previous treatment was 35 months, and was 25 months for the 13 relapsed patients with prior treatment. There was no statistical significance between the median time to first relapse in those who were previously treated and those who did not receive prior therapy (P = .70 by log-rank). Of the 31 patients who had first relapse, 25 had cytopenias requiring therapy, while the remaining 6 without cytopenias were observed. Of the 25, 23 were re-treated with 2-CdA and 2 patients were re-treated with alternative agents (1 with rituximab and the other with 2'-DCF). The patients re-treated with rituximab and 2'-DCF both achieved a CR.

Of the 23 relapsed patients re-treated with 2-CdA, 12 patients (52%) achieved a CR, 7 patients (30%) achieved a PR, 3 patients (13%) had NR, and 1 patient's (4%) response remains to be determined. Of the 12 patients achieving CR, 2 subsequently relapsed (patient no. 1 after 27 months and patient no. 2 after 60 months). Patient no. 1 was re-treated with the immunotoxin BL22 and achieved a CR, and patient no. 2 was re-treated with 2'-DCF, which led to a PR. The second remission for patient no. 1 was shorter than the first remission; however, the second remission was longer than the first remission in patient no. 2. The other 10 patients have been monitored by peripheral blood count without evidence of disease, with a mean follow-up of 9.4 years.

Of the 7 patients who achieved a PR after re-treatment with 2-CdA, 4 were re-treated again. One was treated with rituximab and 2'-DCF resulting in a PR; one was treated with IFN, which led to a PR; one was treated with rituximab, resulting in a PR; and one was treated with 2'-DCF and achieved a CR. The remaining 3 patients were observed by regular monitoring of their peripheral blood counts.

Of the 3 patients who had NR after re-treatment with 2-CdA, 1 died of complications from HCL and 1 died due to complications of metastatic prostate cancer. The third patient was treated with 2'-DCF and achieved a CR that lasted for 72 months (compared with the 35 months of CR after the first cycle of 2-CdA).

Of the 6 relapsed patients who were observed without treatment, 3 have been followed by monitoring of their peripheral blood counts for a mean follow-up of 10.8 years, 1 died of complications from metastatic prostate cancer, and 2 patients were lost to long-term follow-up.

Deaths

After long-term follow-up, 9 patients have died: 2 due to progressive disease, 5 due to complications of other malignancies (3 due to prostate cancer, 1 due to melanoma, and 1 due to colon cancer), and 2 in CR of nonmalignant causes (1 died with normal peripheral blood counts of a presumably unrelated cardiac event 7 months after treatment and the other patient, age 85 years, died of a ruptured abdominal aortic aneurysm 3 years later).

Malignancies

Of the 86 patients treated with 2-CdA, 15 (17%) developed other malignancies (9 prostate cancer, 1 colon cancer, 1 lung cancer, 1 melanoma, 1 thymoma, 1 basal cell cancer, and 1 breast cancer). These are detailed in Table 2. Of these patients, 5 were previously treated before 2-CdA (2 with IFN alone, 2 with splenectomy alone, and 1 with IFN followed by 2'-DCF).
Toxicities

Toxicities from 2-CdA have been previously reported. The majority of acute toxicities included myelosuppression and culture-negative fever. Patients re-treated with 2-CdA had no acute extramedullary toxicities. After treatment with 2-CdA, 2 patients developed neuropathies.

PFS

The estimated PFS rate for the 86 patients treated with 2-CdA is 54% at 12 years (Figure 2). At 12 years, the PFS rate for the 26 previously treated patients is 45%, and is 60% for the 60 previously untreated patients (P = .23, Figure 3). Patients who initially achieved a CR have a PFS rate of 60% at 12 years (Figure 4).

OS

The OS rate for all 86 patients is 87% at 12 years (Figure 5). At 12 years, the OS rate for the 26 previously treated patients is 88%, and is 85% for the 60 previously untreated patients (P = .92, Figure 6). The OS rate at 12 years for the 31 patients who relapsed is 84% (Figure 7). Patients who initially achieved a CR have an OS rate of 90% at 12 years (Figure 8).

Discussion

As reported here, all patients with HCL responded to initial treatment with 2-CdA, with the vast majority of these patients (79%) achieving a CR. Over half of the patients (55%) with a PR following initial treatment with 2-CdA achieved a CR after re-treatment with the drug. Thus, 1 to 2 cycles of 2-CdA are extremely effective in inducing a CR in most patients with HCL. This response is durable as well. The estimated PFS for all patients treated with 2-CdA was 54% and the OS was 87% at 12 years, and patients who initially achieved a CR have even higher PFS and OS rates at 12 years (60% and 90%, respectively). Prior treatment was not statistically significant as a factor in both the PFS and OS. Of the patients who relapsed after 1 cycle of 2-CdA, the most commonly used agent for re-treatment was 2-CdA and the majority of these patients (83%) again responded, with over half of them achieving a CR. Thus, the prognosis of patients with HCL treated with 2-CdA is excellent and is not affected by any history of prior therapy.

Extended follow-up of patients treated with 2-CdA has been previously reported. Goodman et al analyzed 207 patients with HCL treated with 2-CdA and had at least 7 years of follow-up. The CR rate was 95% and the PR rate was 5%, for an overall response rate of 100%. The relapse rate was 37%, and the OS was 97% at 108 months. In this study, shorter disease duration, lower hgb, and higher WBC count at baseline were predictors for treatment failure with 2-CdA. Zinzani et al used 2 different 2-CdA administration modalities (weekly and daily) and reported extended follow-up. Of the 37 eligible patients, the CR rate was 81% and the PR rate was 19% (overall response rate: 100%). At a median follow-up of 122 months, the relapse rate was 27% and the projected 13-year OS was 96%. Jehn et al treated 44 consecutive patients with 2-CdA. Of the patients, 98% achieved a CR, with some of these patients having evidence of residual disease. One patient (2%) achieved a PR (overall response rate: 100%). At a median follow-up of 8.5 years, the relapse rate was 39%, and the overall survival at 12 years after the start of 2-CdA treatment was 79%.
Compared with prior studies, we observed a somewhat lower CR rate after the first cycle of therapy with 2-CdA. This can partly be explained by the criteria for CR reported here. Other studies have not required resolution of splenomegaly or lymphadenopathy by CT scan as criteria for CR. In this study, we required resolution of splenomegaly to 14 cm or less in craniocaudal dimension and resolution of adenopathy to 2 cm or less by both CT scan and physical examination. Several of our patients were classified as achieving a PR based on the presence of such organomegaly that was detected only by CT scanning and would have been missed if only physical examination was required.

Initially, patients who achieved a PR after the first cycle of 2-CdA were offered a second cycle as part of the phase-2 protocol. A total of 6 patients in our study were offered this treatment—2 died in CR, 1 remains in CR to this day, and the final 3 received other therapies, with only 1 of the 3 patients achieving a CR. After evaluation of the data from the initial 43 patients, it was determined that most patients who achieved a PR after the first cycle normalized their peripheral blood counts. This led to offering a second cycle of 2-CdA only after they had documented relapse.

There are conflicting reports in the literature regarding the incidence of other malignancies in patients with HCL. In a study by Au et al, 44 separate malignancies were reported in a total of 36 patients from a cohort of 117 patients for a total incidence of 30.7%. In the M. D. Anderson Cancer Center experience reported by Kurzrock et al, 36 patients (7.4%) developed malignancies after a median follow-up time after diagnosis of 7.1 years. This was not statistically significant when compared with data derived from the Connecticut Tumor Registry. In the Scripps Clinic experience reported by Goodman et al, 48 second malignancies developed in 22% of HCL patients treated with 2-CdA. This represented a low to moderate (2.03-fold) increase in the development of a second neoplasm. However, only 3 patients developed a malignancy after exposure to 2-CdA, suggesting that factors other than 2-CdA were contributing to the risk of secondary malignancies.

In this study, 15 (17%) of the 86 patients treated with 2-CdA developed other malignancies. Most of these malignancies were solid tumors, with prostate cancer being the most common. No hematologic malignancies developed after exposure to 2-CdA. The percentage of patients that developed malignancies in our population is somewhat lower than the percentage observed by Goodman et al but is higher than what would be expected when compared with an age-matched cohort in the Surveillance, Epidemiology, and End Results (SEER) database. Whether this is related to HCL, treatment of the disease, or the result of confounding variables is unclear.

As most patients with HCL continue to do well for many years without recurrence, one question that arises is whether they are cured of their disease or are simply in a long-term remission. This question continues to remain unanswered. In their study, Goodman et al reported no obvious plateau of the time-to-treatment failure curve. We also observed no plateau in the PFS curve after follow-up of close to 14 years, suggesting that late relapses do occur. However, most patients with HCL continue to survive and do not die as a result of their disease. Additional studies following...
HCL patients treated with 2-CdA for even longer periods of time are needed. Meanwhile, care of these patients should be focused on detection of other malignancies and medical conditions as dictated by current screening and treatment guidelines.

Future directions for treatment of HCL continue to be investigated. Further investigation is warranted to determine whether PFS can be improved with eradication of minimal residual disease (MRD). We previously reported a relapse-free survival difference between patients who had MRD in their bone marrow compared with those who did not. Whether eradication of MRD with agents such as rituximab would lead to improvements in PFS and OS is untested, but warrants further study. Rituximab has an advantage over purine analogs such as 2-CdA and 2’-DCF in that it is less immunosuppressive. Rituximab is also an option for patients with purine analog-resistant disease. Thomas et al reported an 80% overall response rate (53% CR, 13% CR-MRD, 13% PR) in purine analog–resistant disease. Thomas et al reported an 80% overall response rate (53% CR, 13% CR-MRD, 13% PR) in patients with relapsed or primary refractory HCL after nucleoside analog therapy who received 8 to 12 doses of weekly rituximab.16 Excellent results have been reported by Kreitman et al with the use of BL22, a recombinant immunotoxin containing the variable portion (fv) of the monoclonal antibody to CD22 fused to a fragment of Pseudomonas exotoxin.17 In previously treated HCL patients given BL22, the overall response rate was 80%, with 69% of patients achieving a CR. Toxicity in these patients included a cytokine release syndrome and the development of a reversible hemolytic-uremic syndrome in 2 patients.

In summary, long-term follow-up of patients with HCL treated with 2-CdA shows that this agent is a safe and highly effective treatment for this disease. The majority of patients enjoy long-term remission. Patients who relapse have several options available, including another cycle of 2-CdA, treatment with alternative purine analogs, or treatment with novel agents such as rituximab and BL22. Based on this long-term experience with 2-CdA in HCL, purine analogs such as 2-CdA should be agents of choice in the initial treatment of HCL. Whether patients who continue to be in long-term remission after treatment with 2-CdA are cured of their disease remains to be determined. However, patients can be assured of excellent OS after treatment with 2-CdA.

References

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