Complete Hematologic Remissions Induced by 2-Chlorodeoxyadenosine in Children With Newly Diagnosed Acute Myeloid Leukemia


The majority of children with acute myeloid leukemia (AML) who are treated exclusively with chemotherapy die of progressive disease. Improvement in outcome will likely require new active drugs capable of eradicating resistant blast cells early in the clinical course. We therefore assessed the cytoreductive potential of 2-chlorodeoxyadenosine (2-CdA), a halogenated purine analogue, in 22 consecutive children with newly diagnosed AML. The drug was administered as a single 120-hour continuous infusion (8.9 mg/m^2 of body surface area per day) before the introduction of standard remission induction therapy. Six patients (27%) had complete hematologic remissions by a median of 21 days after treatment with the nucleoside (range, 14 to 33 days). Seven others had partial responses, yielding a total response rate of 59%. The drug also eliminated leukemic cells from cerebrospinal fluid in 4 of the 6 patients tested. Concentrations of 2-CdA in cerebrospinal fluid on day 5 after the initiation of treatment ranged from 12.4% to 38.0% (mean, 22.7%) of the steady-state plasma concentrations. Severe but reversible myelosuppression and thrombocytopenia developed in all patients. Analysis of factors that may have influenced the complete remission rate suggested a better outcome in patients with myeloblastic leukemia (M0-M2 subtypes in the revised French-American-British classification system). These results demonstrate clinically significant activity by 2-CdA against previously untreated AML in children, including leukemic blast cells in the central nervous system. Its use in combination chemotherapy may improve the outlook for patients with this often fatal hematologic cancer.

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MATERIALS AND METHODS

Patients. Children or young adults with an unequivocal diagnosis of de novo AML and adequate renal and hepatic function (serum creatinine and bilirubin levels ≤2 mg/dL) were eligible for the study. The diagnosis of AML was made by standard morphologic and cytochemical criteria of the modified French-American-British (FAB) Cooperative Group. Patients with FAB M3 leukemia were excluded. The presenting characteristics of the 22 patients who met all eligibility requirements are summarized in Table I. These 10 male and 12 female patients had a median age of 7.0 years (range, 0.6 to 18.8 years) and a median leukocyte count of 11.1 × 10^9/L.

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Table 1. Characteristics of the 22 Patients Before and After Treatment With 2-CdA

<table>
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<tr>
<th>Patient No.</th>
<th>Leukocyte Count (10^3/μL)</th>
<th>AML Subtype</th>
<th>Partial Karyotype</th>
<th>% Blasts in S-Phase</th>
<th>Bone Marrow Findings</th>
<th>Response</th>
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<td>Posttreatment</td>
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<td>2</td>
<td>F14.0</td>
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<td>(8;21)</td>
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<td>100</td>
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<td>3</td>
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<td>(8;21)</td>
<td>6.6</td>
<td>56</td>
</tr>
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<td>F7.3</td>
<td>9.1</td>
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<td>(8;21)</td>
<td>15.3</td>
<td>74</td>
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<tr>
<td>5</td>
<td>F9.3</td>
<td>4.1</td>
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<td>(9;11)</td>
<td>3.9</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
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<td>M5</td>
<td>(9;11)</td>
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<td>89</td>
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<td>(6;21)</td>
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<tr>
<td>8</td>
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<td>(1;22)</td>
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<td>M7</td>
<td>del(13)</td>
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<td>70</td>
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<td>81</td>
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<td>M4</td>
<td>inv16</td>
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<td>64</td>
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<tr>
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<td>6.4</td>
<td>M7</td>
<td>(7;11)</td>
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<td>64</td>
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<tr>
<td>22</td>
<td>M16.8</td>
<td>49.7</td>
<td>M1</td>
<td>Normal</td>
<td>5.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; PR, partial remission; NR, no response; NA, not available.
* FAB classification.

Results: A complete hematologic remission was indicated by a cellular marrow with less than 5% blast cells and the normalization of peripheral blood cell counts by 30 days posttreatment. A partial remission was defined as a decrease in leukemic bone marrow cellularity to 5% to 25% blast cells with at least 15% erythroid elements and approximately 25% normal granulocyte forms. A 50% reduction in the circulating blast cell count, with or without a reduction in marrow cellularity, was considered evidence for an antileukemic effect but did not constitute a clinical response.

Statistical analysis. The relationship of patient characteristics—sex, age, leukocyte count, FAB leukemia subtype, karyotype, and the percentage of bone marrow blast cells in S phase—to clinical responses was tested with Fisher's exact test. Pretreatment and day-5 blast cell counts were compared with the Wilcoxon sign rank test. Ninety-five percent confidence intervals were calculated for use with overall response rates.22

RESULTS

Circulating blast cells decreased in all patients during the 5-day infusion of 2-CdA, disappearing altogether in 11 patients (Fig 1). Analysis of bone marrow collected on day 10 posttreatment showed fewer than 5% blasts in six marrow samples. Each of these patients attained a complete hematologic remission within 14 to 33 days (median, 21 days). Their times to recovery of neutrophil counts ≥500/μL and platelet counts ≥50 × 10^3/μL ranged from 17 to 31 days (median, 22 days) and from 0 to 28 days (median, 14 days), respectively. Seven other patients had partial remissions for a total response rate of 59% (95% confidence interval, 36% to 79%). It may be important that 3 of the patients considered to be partial responders (nos. 7, 9, and 11) had fewer than

(range, 3.3 to 130). Distributions of leukemia subtypes (excluding M3) and chromosomal features were characteristic of AML patients in general.23 This study was approved by the St Jude Hospital Institutional Review Board; enrollment was contingent on informed consent of the patients or their parents.

Treatment plan. 2-CdA was synthesized and purified at St Jude Children’s Research Hospital, as previously described.29 Solutions for clinical use were prepared in isotonic saline at a concentration of 1 mg/mL, sterilized by ultrafiltration, and stored at 5°C. Each for clinical use were prepared in isotonic saline at a concentration

Conventional therapy. The planned dosage was 8.9 mg/m² of body surface area per day, administered as a continuous intravenous infusion over 120 hours, a regimen suggested by results of our phase I and II studies in patients with relapsed leukemia.30 To ensure consistent drug delivery, we diluted each daily dose of drug in 240 mL of 0.45% sodium chloride in 5% dextrose water and administered the solution with an infusion pump system at a rate of 10 mL/hour.

During the 5-day treatment, patients were monitored for changes in blood cell counts, serum electrolyte levels, blood urea nitrogen level, creatinine level, and coagulation profile. Toxicity was graded according to standards of the National Cancer Institute (available on request). Blood and cerebrospinal fluid samples for pharmacokinetic studies were collected and analyzed by previously described methods.29 Bone marrow aspirates and biopsy samples were taken 10 days after treatment to assess the effectiveness of 2-CdA against leukemia cells in the marrow. Patients with persistent leukemia were treated immediately with cytarabine, etoposide, and daunorubicin. For those without evidence of leukemia, marrow biopsies were repeated at weekly intervals (up to 33 days) to document remission status. On completion of standard remission therapy, patients were given the option of bone marrow transplantation or continued chemotherapy with high-dose cytarabine and daunorubicin. This report deals primarily with responses to 2-CdA.
2-CdA has been regarded by many as an antilymphocyte drug exclusively. This perception grew from observations that lymphocytes contain unusually high concentrations of deoxycytidine kinase, the enzyme primarily (but not solely) responsible for the first step in phosphorylation of 2-CdA; whereas peripheral granulocytes have low concentrations of the kinase. To the contrary, results of in vitro studies indicate that the purine analogue is rapidly phosphorylated by myeloid cell lines and by leukemic blasts from AML patients, and that human cell lines of myeloid origin, as well as human peripheral monocytes, are quite sensitive to this agent. We were sufficiently encouraged by these findings to undertake clinical trials of 2-CdA in children with AML.

In the present study, more than half of 22 previously untreated patients responded to 2-CdA administered as a 5-day continuous infusion. The total response rate of 59%, with a complete remission rate of 27%, compares favorably to results obtained with cytarabine, daunorubicin, or etoposide, the three agents most commonly used to induce remission in AML. Quite likely, additional complete remissions would have been induced had the patients received a second course...
of 2-CdA, as in our phase II study with relapsed AML. Three of the patients judged to be partial responders on the strength of day-10 bone marrow findings in fact had fewer than 10% marrow blasts and may have entered complete remission with longer follow-up, before the instigation of standard treatment. Whether 2-CdA would produce equivalent responses in adults with AML is unclear. In a preliminary analysis, Vahdat and Warrell noted decreases in peripheral blood blasts but no objective marrow responses among 14 adults with relapsed AML who received 2-CdA. The drug also eradicated leukemic blast cells from the cerebrospinal fluid in 4 of 6 evaluable patients. Its ability to cross the blood-brain barrier into the central nervous system was suggested by an isolated finding in our phase II trial and by a recent report from Saven et al in which 2-CdA was detected in cerebrospinal fluid after systemic drug administration. Cerebrospinal fluid levels of 2-CdA attained in the present study were in the range that produces 50% inhibition of dividing myeloid cells in vitro. Thus, the nucleoside may be useful in treating patients with meningeal involvement.

Patients with untreated AML have a low percentage of replicating blast cells in their bone marrow. Hence, a large fraction of the leukemic clone may be initially resistant to treatment with S-phase-specific agents such as cytarabine.

A unique feature of 2-CdA is its strong activity against resting cells, a property that has proved useful in the treatment of indolent lymphoproliferative disorders. We postulate that the non–cycle-specific activity of this agent accounts for much of its potency against leukemic myeloid cells.

Other therapeutic nucleosides that have undergone clinical testing in patients with acute leukemia include fludarabine and deoxycoformycin. Although showing impressive anti-leukemic activity, these agents have had limited application because of their unpredictable neurotoxicity. The major form of toxicity produced by 2-CdA was dose-related myelosuppression. Despite episodes of severe neutropenia in all patients, there were few serious infections that could be attributed to the nucleoside analogue. We attribute this outcome to the absence of damage to extramedullary tissues, such as the mucosal barrier, that protect the neutropenic patient from opportunistic pathogens. Moreover, in contrast to cytarabine and the anthracyclines, 2-CdA produced only a single case of severe mucositis and did not appear to predispose patients to more severe lymphocytopenia during multiagent induction therapy. A less favorable toxicity profile might be expected when 2-CdA is integrated into intensive combination regimens.

The best method for administering 2-CdA remains uncertain. In our phase I study, intracellular nucleotide disappearance rates were high (α- and β-, half-lives of 1.29 and 2.47 hours, respectively), suggesting that continuous infusion of the analogue would produce greater cell kill. However, recent reports from Liliemark and Juliusson indicate a terminal half-life of 6.3 hours after a 2-hour infusion of 2-CdA, which may permit the drug to be administered as an intermittent infusion without loss of antitumor activity. An intermittent dosing schedule that achieves a steady-state plasma concentration exceeding the tumoricidal concentration would be desirable. It will be important to investigate continuous and intermittent infusions of 2-CdA for their relationship to the plasma drug concentrations and active intracellular metabolites. Alternative treatment schedules and routes of administration will be needed to facilitate wider use of this agent, especially in outpatient settings.

The decision to test 2-CdA in previously untreated patients was prompted by evidence that classic phase II trials can
lead to erroneous estimates of drug activity. Because of concerns over possible leukemic progression caused by the delay in standard therapy, we elected to administer only a single course of 2-CdA. We find it reassuring that all 6 patients who entered complete remission on 2-CdA treatment maintained their responses throughout the period of standard chemotherapy, and that all 7 with partial responses eventually attained complete remission status with use of additional agents. Although follow-up is relatively short, half of the patients who achieved complete remission remain disease-free at a median of 18 months after bone marrow transplantation, a result similar to the experience in larger, frontline trials.

These results make 2-CdA an attractive candidate for new regimens of combination chemotherapy. To obtain maximal cell kill, we suggest early use of the purine analogue with S-phase-specific, non-cross-resistant drugs such as etoposide or daunorubicin. It will also be important to administer a second course of 2-CdA during the remission induction phase. This added drug exposure would allow greater accumulation of DNA strand breaks in resting cells and thus could be expected to improve the clinical response rate. In our phase II trial in previously treated patients, the number of complete remissions approximately doubled after a second course of 2-CdA. A firmer basis for selection of drug combinations including 2-CdA should come from preclinical studies now under way.

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Complete hematologic remissions induced by 2-chlorodeoxyadenosine in children with newly diagnosed acute myeloid leukemia

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