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/m² 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 1. 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 × 10⁹/L.

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consistent drug delivery, we diluted each daily dose of drug in 240 mL of 0.45% sodium chloride in water, sterilized by ultrafiltration, and stored at 5°C. Each infusion over 120 hours, a regimen suggested by results of our phase II studies,35-39 Solutions for clinical use were prepared in isotonic saline at a concentration ranging from 0.4% to 10%.

Informed consent of the patients or their parents was obtained before treatment. A partial remission was defined as a decrease in leukemic blast cell counts with or without a reduction in marrow cellularity, was considered evidence for an antileukemic effect but did not constitute a clinical response.6

**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 × 10^4/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

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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age (yr)</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>% Blasts Pretreatment</th>
<th>% Blasts Posttreatment</th>
<th>% Marrow Cellularity Pretreatment</th>
<th>% Marrow Cellularity Posttreatment</th>
<th>2-CdA Treatment Induction</th>
<th>Response</th>
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<tbody>
<tr>
<td>1</td>
<td>M5/3</td>
<td>4.3</td>
<td>M0</td>
<td>t(3;11)</td>
<td>11.0</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>30-40</td>
<td>CR</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F/14.0</td>
<td>109.2</td>
<td>M2</td>
<td>t(8;21)</td>
<td>3.9</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>20-25</td>
<td>CR</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M/3.8</td>
<td>12.8</td>
<td>M2</td>
<td>t(8;21)</td>
<td>6.6</td>
<td>56</td>
<td>0</td>
<td>100</td>
<td>95</td>
<td>CR</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F/7.3</td>
<td>9.1</td>
<td>M2</td>
<td>t(8;21)</td>
<td>15.3</td>
<td>74</td>
<td>3.5</td>
<td>95</td>
<td>25-30</td>
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</tr>
<tr>
<td>5</td>
<td>F/9.3</td>
<td>4.1</td>
<td>M5</td>
<td>t(9;11)</td>
<td>3.9</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>10</td>
<td>CR</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F/0.6</td>
<td>9.4</td>
<td>M5</td>
<td>t(9;11)</td>
<td>NA</td>
<td>89</td>
<td>1</td>
<td>100</td>
<td>40</td>
<td>CR</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M/13.3</td>
<td>14.7</td>
<td>M2</td>
<td>t(8;21)</td>
<td>3.2</td>
<td>57</td>
<td>9</td>
<td>100</td>
<td>10</td>
<td>PR</td>
<td>CR</td>
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<tr>
<td>8</td>
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<td>CR</td>
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<tr>
<td>9</td>
<td>F/3.2</td>
<td>4.6</td>
<td>M4</td>
<td>+4,+8</td>
<td>17.5</td>
<td>63</td>
<td>7</td>
<td>100</td>
<td>30-35</td>
<td>PR</td>
<td>CR</td>
<td></td>
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<tr>
<td>10</td>
<td>F/1.3</td>
<td>50.8</td>
<td>M4</td>
<td>inv16</td>
<td>6.8</td>
<td>58</td>
<td>15</td>
<td>100</td>
<td>70</td>
<td>PR</td>
<td>CR</td>
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<tr>
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<td>F/1.0</td>
<td>5.4</td>
<td>M5</td>
<td>t(9;11)</td>
<td>9.8</td>
<td>39</td>
<td>5</td>
<td>100</td>
<td>90</td>
<td>PR</td>
<td>CR</td>
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<tr>
<td>12</td>
<td>M/2.8</td>
<td>13.9</td>
<td>M4</td>
<td>inv16</td>
<td>14.6</td>
<td>70</td>
<td>10</td>
<td>100</td>
<td>90</td>
<td>PR</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F/0.8</td>
<td>8.7</td>
<td>M7</td>
<td>t(1;22)</td>
<td>NA</td>
<td>33</td>
<td>10</td>
<td>100</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>M/2.9</td>
<td>13.3</td>
<td>M7</td>
<td>del(13)</td>
<td>3.6</td>
<td>70</td>
<td>66</td>
<td>100</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
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<td>iso8q</td>
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<td>16</td>
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<td>83</td>
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<td>CR</td>
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<td>18</td>
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<td>50</td>
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<td>t(7;11)</td>
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<td>20</td>
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<td>NR</td>
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<td>M7</td>
<td>+8</td>
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<td>10</td>
<td>NR</td>
<td>CR</td>
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<td>22</td>
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<td>Normal</td>
<td>5.2</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>CR</td>
<td>CR</td>
<td></td>
</tr>
</tbody>
</table>

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

* FAB classification.

(range, 3.3 to 130). Distributions of leukemia subtypes (excluding M3) and chromosomal features were characteristic of AML patients in general.25 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.27,29 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 patient received a single course of the purine analogue before any chemotherapy. A partial remission was defined as a decrease in leukemic blast cell counts with or without a reduction in marrow cellularity, was considered evidence for an antileukemic effect but did not constitute a clinical response.6

**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 variables were compared with the Wilcoxon sign rank test. Ninety-five percent confidence intervals were calculated for use with overall response rates.32

**Response criteria.** 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 marrow cellularity to 5% to 25% blast cells with at least 15% erythrocyte 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.
2-CoA

percentage of blast cells in S-phase of the cell cycle. The
tion in our patients, as might be expected from reports that
blast cells in
result was statistically inconclusive. A higher percentage of
complete remission rate was higher among patients with
myeloblastic leukemia (MO-M2 classifications) compared
leukocyte count, FAB leukemia subtype, karyotype, and the
remission after multiagent induction treatment (Table
months).
Nine patients (41%) remain in remission after autologous
responses to 2-CdA, we compared response rates by sex, age,
other factors examined in this analysis failed to
with those with other subtypes (4 of 9
S
v
2
of
13), although,
small number of cases in some FAB categories, the
result was statistically inconclusive. A higher percentage of
blast cells in S phase, did not correlate with remission induc-
tion in our patients, as might be expected from reports that
2-CdA kills not only dividing cells but also resting cells in
vitro. Other factors examined in this analysis failed to
show any relationship to the remission induction rate.

10% blast cells in bone marrow on day 10 of 2-CdA therapy.
Each of the 6 complete responders, each of the 7 partial
responders, and 3 of the 9 nonresponders were in complete
remission after multiagent induction treatment (Table 1).
Nine patients (41%) remain in remission after autologous
or allogeneic marrow transplantation (median follow-up, 18
months).

To identify factors that may have influenced clinical re-
cponses to 2-CdA, we compared response rates by sex, age,
leukocyte count, FAB leukemia subtype, karyotype, and the
percentage of blast cells in S-phase of the cell cycle. The
complete remission rate was higher among patients with
myeloblastic leukemia (M0-M2 classifications) compared
with those with other subtypes (4 of 9 v 2 of 13), although,
with the small number of cases in some FAB categories, the
result was statistically inconclusive. A higher percentage of
blast cells in S phase, did not correlate with remission induc-
tion in our patients, as might be expected from reports that
2-CdA kills not only dividing cells but also resting cells in
vitro. Other factors examined in this analysis failed to
show any relationship to the remission induction rate.

Because of evidence that 2-CdA penetrates the blood-
stream barrier, we sought to assess its effects against leukemic
cells in the central nervous system. Table 2 shows the
percentages of leukocytes in the cerebrospinal fluid of 6
of the 7 patients who presented with meningeal leukemia.
Leukocyte counts were reduced to negligible levels in all
cases, and blast cells were eradicated in 4. Plasma and
cerebrospinal fluid concentrations of 2-CdA were available for
6 of the 7 patients presenting with meningeal involvement.
On day 5 of the continuous infusion, drug concentrations
in cerebrospinal fluid ranged from 12.4% to 38.0% (mean,
22.7%) of steady-state plasma concentrations.
The spectrum of toxic effects associated with 2-CdA treat-
ment is shown in Table 3. Severe but reversible myelosup-
pression and thrombocytopenia were noted in all patients.
There were febrile neutropenic episodes of unknown origin
in 10 patients, but none was associated with fatal complica-
tions. Five patients had documented infections: sepsis (1),
cellulitis (2), otitis media (1), and intravenous catheter track
infection (1). There were no unusual infections caused by
opportunist pathogens such as Pneumocystis pneumonia or
cytomegalovirus. Lymphocytopenia (<1,000 cells/μL) de-
veloped in 17 of 22 patients before the instigation of
multiagent chemotherapy and persisted in 9 of these until
marrow transplantation. One child with acute monoblastic
leukemia presented with acute renal failure that worsened
after she received 2-CdA. Two patients had modest increases
in hepatic transaminase levels. Only 1 patient developed
significant mucositis (grade 3). None of the observed toxic
effects limited the protocol-specified dosage or the tolerance
to subsequent therapy.
A single case of Aspergillus pneumonia was observed,
and three other fungal infections were clinically suspected
but unproven (2 pneumonias and 1 hepatic lesion) during
subsequent multiagent induction therapy.

DISCUSSION

2-CdA has been regarded by many as an antilymphocyte
drug exclusively. This perception grew from observa-
tions 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 concentra-
tions of the kinase. To the contrary, results of in vitro
studies indicate that the purine analogue is rapidly phosphor-
ylated 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 find-
ings to undertake clinical trials of 2-CdA in children with
AML.

In the present study, more than half of 22 previously un-
treated 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 re-
sults 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
Table 2. 2-CdA Activity Against AML in the Central Nervous System

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Subtype*</th>
<th>Leukocytes Pretreatment</th>
<th>% Blasts Pretreatment</th>
<th>Leukocytes Posttreatment</th>
<th>% Blasts Posttreatment</th>
<th>Drug Concentration (nmol/L) on Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>M5</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>M5</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>76.9 ND 7.25</td>
</tr>
<tr>
<td>1c</td>
<td>M4</td>
<td>5</td>
<td>16</td>
<td>1</td>
<td>4</td>
<td>26.2 5.75</td>
</tr>
<tr>
<td>11</td>
<td>M5</td>
<td>13</td>
<td>49</td>
<td>2</td>
<td>0</td>
<td>47.9 2.65</td>
</tr>
<tr>
<td>12</td>
<td>M4</td>
<td>13</td>
<td>19</td>
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<td>22</td>
<td>M1</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; ND, not done.
* FAB classification.
† Number per microliter of CSF.

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 Warrell13 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 and enter the central nervous system was suggested by an isolated finding in our phase II trial29 and by a recent report from Saven et al39 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.6 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.4 Hence, a large fraction of the leukemic clone may be initially resistant to treatment with S-phase-specific agents such as cytarabine.

Table 3. Toxicity Associated With 2-CdA Treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Episodes*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>1</td>
</tr>
<tr>
<td>Liver enzyme abnormalities</td>
<td>2</td>
</tr>
<tr>
<td>Fever and neutropenia</td>
<td>10</td>
</tr>
<tr>
<td>Documented infection</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>19</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22</td>
</tr>
</tbody>
</table>

* Toxic reactions were limited to a single episode per child.
† Grade 3 or 4 by National Cancer Institute guidelines.
lead to erroneous estimates of drug activity.\textsuperscript{42-44} 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.\textsuperscript{45}

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 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\textsuperscript{11,13} 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.\textsuperscript{29} A firmer basis for selection of drug combinations including 2-CdA should come from preclinical studies now under way.

**ACKNOWLEDGMENT**

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

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