High-Dose Cytosine Arabinoside Therapy for Refractory Leukemia


Fifty-seven patients with refractory acute leukemia were treated with high-dose cytosine arabinoside to establish the maximum tolerated dose and duration and to determine the antileukemic activity. The maximum tolerated regimen was found to be 3 g/sq m every 12 hr for 6 days. At this dose, nonhematologic toxicity was limited to conjunctivitis in approximately half of the patients, and liver toxicity (transient elevations in transaminase, alkaline phosphatase, or bilirubin) was frequently observed, but neither was dose-limiting. Extending the duration of treatment to 8 days resulted in excessive diarrhea and skin toxicity (painful erythema with bullae), while increasing the dose to 4.5 g/sq m q. 12 hr for 6 days resulted in severe cerebellar toxicity. Myelosuppression was severe, but was not related to the intensity of treatment; granulocyte recovery occurred a median of 28 days (range 22-40 days) after initiating therapy, and platelet recovery occurred after a median of 25 days (range 16-41 days). Antileukemic activity was evaluable in the 46 patients who survived at least 3 wk. Complete remissions were obtained in 1 of 6 patients with chronic myelogenous leukemia (CML) in accelerated phase and 1 of 3 acute lymphoblastic leukemia (ALL) patients. A more detailed analysis of response was possible for the 37 evaluable patients with acute nonlymphoblastic leukemia: 70% of these patients responded, with 51% complete remissions. The median unmaintained response was 4 mo (range 2-26+ mo). The complete response rate was higher in patients who received at least 12 doses of high-dose cytosine arabinoside compared to shorter regimens [17/28 (61%) versus 2/9 (22%), p < 0.05]. Resistance to cytosine arabinoside in conventional doses was documented in 11 patients, 5 of whom responded (2 complete remissions) to high-dose regimens. We conclude that high-dose cytosine arabinoside in the maximally tolerated regimen of 3 g/sq m every 12 hr for 6 days has substantial antileukemic activity in patients refractory to standard therapy. Durable unmaintained remissions can be achieved, even in patients who fail to respond to cytosine arabinoside in conventional doses.

Cytosine arabinoside is an important drug in the treatment of acute nonlymphoblastic leukemia, with a 30% response rate when used as a single agent in untreated patients. The mechanisms responsible for resistance to cytosine arabinoside are poorly defined, but in some in vitro models, resistance can be overcome by increased doses. In a recent report, Rudnick et al. used high doses of cytosine arabinoside for patients with leukemia refractory to conventional chemotherapy. Cytosine arabinoside was given at a dose of 1.0-7.5 g/sq m every 12 hr for 1-4 doses, representing a substantial increase over the usual dose of 0.1-0.2 g/sq m. Toxicity was not severe, and one patient achieved a complete response, suggesting that resistance to cytosine arabinoside could be overcome by large doses given on an intermittent intravenous bolus schedule. Based on these preliminary findings, we set out to establish the maximum tolerated dose and duration of cytosine arabinoside given intermittently on a 12-hr schedule and to determine the antileukemic activity of cytosine arabinoside at the maximum tolerated dose.

MATERIALS AND METHODS

Patient Characteristics

Fifty-seven patients with refractory acute leukemia were studied. The patients were considered refractory to conventional therapy, since the expected response rate in these patients was less than 25%. The median age was 38 yr (range 16-76 yr). Disease categories included acute nonlymphoblastic leukemia in relapse (46 patients), acute lymphoblastic leukemia in relapse (4 patients), and chronic myelogenous leukemia in accelerated phase (7 patients). Forty-five patients had received conventional doses of cytosine arabinoside; 14 patients were considered to be resistant to conventional doses, having failed one or more courses just before treatment with high-dose cytosine arabinoside. The four patients with acute lymphoblastic leukemia were all null cell by surface markers. They were older children and young adults (ages 15, 20, 22, and 23). It was the second induction attempt for two patients, and the third and fourth attempt for the remaining two patients. The seven patients with chronic myelogenous leukemia were all Philadelphia-chromosome-positive and had been treated with hydroxyurea or busulfan during the chronic phase. The accelerated phase was defined as an increasing requirement of chemotherapy for control, an increasing eosinophilia, increasing hepatosplenomegaly, thrombocytopenia, greater than 20% progranulocytes and blasts, evidence of a cytogenetic clonal evolution, or myelofibrosis. The study protocols were reviewed by each institution's Review Committee for Human Experimentation. Patients gave informed consent.

Study Design

The initial schedule of cytosine arabinoside was 3 g/sq m intravenously every 12 hr for 2 days (4 doses). In subsequent groups of patients, escalation by 4 doses was made as permitted by toxicity. The maximum tolerated duration was defined as the level at which 0-1 episodes of fatal or life-threatening toxicity occurred. Patients were treated with high-dose cytosine arabinoside to establish the maximum tolerated dose and duration and to determine the antileukemic activity. The maximum tolerated regimen was found to be 3 g/sq m every 12 hr for 6 days. At this dose, nonhematologic toxicity was limited to conjunctivitis in approximately half of the patients, and liver toxicity (transient elevations in transaminase, alkaline phosphatase, or bilirubin) was frequently observed, but neither was dose-limiting. Extending the duration of treatment to 8 days resulted in excessive diarrhea and skin toxicity (painful erythema with bullae), while increasing the dose to 4.5 g/sq m q. 12 hr for 6 days resulted in severe cerebellar toxicity. Myelosuppression was severe, but was not related to the intensity of treatment; granulocyte recovery occurred a median of 28 days (range 22-40 days) after initiating therapy, and platelet recovery occurred after a median of 25 days (range 16-41 days). Antileukemic activity was evaluable in the 46 patients who survived at least 3 wk. Complete remissions were obtained in 1 of 6 patients with chronic myelogenous leukemia (CML) in accelerated phase and 1 of 3 acute lymphoblastic leukemia (ALL) patients. A more detailed analysis of response was possible for the 37 evaluable patients with acute nonlymphoblastic leukemia: 70% of these patients responded, with 51% complete remissions. The median unmaintained response was 4 mo (range 2-26+ mo). The complete response rate was higher in patients who received at least 12 doses of high-dose cytosine arabinoside compared to shorter regimens [17/28 (61%) versus 2/9 (22%), p < 0.05]. Resistance to cytosine arabinoside in conventional doses was documented in 11 patients, 5 of whom responded (2 complete remissions) to high-dose regimens. We conclude that high-dose cytosine arabinoside in the maximally tolerated regimen of 3 g/sq m every 12 hr for 6 days has substantial antileukemic activity in patients refractory to standard therapy. Durable unmaintained remissions can be achieved, even in patients who fail to respond to cytosine arabinoside in conventional doses.

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R.H.H. is a Scholar, Leukemia Society of America; S.N.W., H.M.L., and G.L.P. are American Cancer Society Junior Faculty Clinical Fellows.

Supported in part by NIH grant ROI-CA-15584-05.

Submitted July 8, 1982; accepted February 24, 1983.

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0006-4971/83/6202-0021$01.00/0

suppression) occurred in 10 patients. Accordingly, the duration of treatment with cytosine arabinoside (3 g/sq m) was increased from 2 days to 4, 6, and then 12 days. When the 6-day (12-dose) regimen was found to be the maximum duration, the maximum dose was to be determined by 50% increments until dose-limiting toxicity was encountered. This phase of the study was completed when 6 patients receiving 12 doses of 4.5 g/sq m experienced toxicity to the central nervous system. All subsequent patients were treated with 3 g/sq m for 12 doses to further determine the antileukemic effect.

Preparation and Administration of Cytosine Arabinoside

Cytosine arabinoside was reconstituted (without the supplied diluent), using 300 ml 0.9% preservative-free normal saline, and was given by 1-hr intravenous infusion every 12 hr.

Toxicity Grading

A scale of 0–4 was used to record organ toxicity. In general, grade 0 was the absence of toxicity; grade 1, minimal dysfunction; grade 2, moderate dysfunction; grade 3, severe but reversible; grade 4, life-threatening, irreversible, or fatal. The toxicity grading for each organ system is given in Table 1.

Response

Complete remission (CR). Less than 5% blasts in a normocellular bone marrow and normal peripheral blood counts.

Partial remission (PR). Defined as 5%–15% blasts in the bone marrow with normal peripheral blood counts.

Treatment failures. Defined as persistence of leukemia with therapy or recovery from aplasia with greater than 15% blasts in the bone marrow. Patients who died within 2–1 days of initiating therapy or recovery from aplasia with greater than 15% blasts in the bone marrow and normal peripheral blood counts. They were considered failures.

Duration of response. This was computed from the first day of treatment to the date of bone marrow relapse. For patients with a partial response, the duration of response ended when bone marrow blasts exceeded 15%. Patient entry began on February 1, 1978, and follow-up is current as of January 1, 1982.

Statistics

Comparisons among groups were performed using the Fisher exact test.

RESULTS

Toxicity

Table 2 summarizes the systemic toxicity for high-dose cytosine arabinoside, related to dose and duration of therapy. Neither renal nor pulmonary toxicity occurred. Anaphylaxis was not observed. The remainder of the side effects are described below.

Ophthalmologic toxicity was observed in 27 patients (47%) but was not severe and was completely reversible. The manifestations were conjunctivitis and photophobia, which began 4–8 days after initiating cytosine arabinoside therapy and lasted a median of 4 days (range 2–9 days). The incidence of conjunctivitis and photophobia increased with increasing duration of therapy. With regimens of 2–4 days, only 2 of 12 patients exhibited eye toxicity, while for regimens of 6–8 days, 22 of 26 patients were affected (p < 0.001). It was found that the institution of glucocorticoid eye drops (0.1% dexamethasone, 2 drops each eye every 6–8 hr) before the first dose of cytosine arabinoside would ameliorate or prevent the conjunctivitis and photophobia.

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Eye</th>
<th>Skin</th>
<th>Central Nervous System</th>
<th>Nausea/Vomiting</th>
<th>Diarrhea</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Conjunctivitis and photophobia absent</td>
<td>Normal</td>
<td>Cerebellar or cerebral dysfunction absent</td>
<td>None</td>
<td>None</td>
<td>Normal tests of liver function</td>
</tr>
<tr>
<td>1</td>
<td>Mild; requires no therapy</td>
<td>Maculopapular rash or erythroderma &lt;25% body</td>
<td>Mild; able to carry out activities of normal living</td>
<td>Symptoms controlled with antiemetics</td>
<td>&lt;500 ml/day (&lt;5 stools/day)</td>
<td>Elevation &lt;2 x normal</td>
</tr>
<tr>
<td>2</td>
<td>Moderate; use of eye drops necessary</td>
<td>25%–50% body involved</td>
<td>&lt;50% decline in function; some assistance necessary to carry out activities of normal living</td>
<td>Symptoms not controlled with antiemetics during infusion</td>
<td>500–1,000 ml/day (5–10 stools/day)</td>
<td>Elevation 2–5 x normal</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic &gt;1 wk despite therapy</td>
<td>Dry desquamation, &gt;50% body involved</td>
<td>&gt;50% decline in function; assistance necessary for normal activities</td>
<td>Symptoms persist &gt;2 days after end of treatment</td>
<td>&gt;1,000 ml/day (&gt;10 stools/day)</td>
<td>Elevation &gt;5 x normal, reversible</td>
</tr>
<tr>
<td>4</td>
<td>Symptomatic, &gt;1 mo or vision permanently impaired</td>
<td>Bullae; toxic epidermal necrolysis</td>
<td>Irreversible or coma or fatal</td>
<td>Mallory-Weiss tear</td>
<td>Intestinal perforation or life-threatening hemorrhage</td>
<td>Coma or death</td>
</tr>
</tbody>
</table>

*See text for details.
photophobia. Thus, for all patients on 6- and 8-day regimens, 22/26 (85%) had eye problems if no eye drops were used, compared to an incidence of 3/19 (16%) with eye drops (p < 0.001). Slit-lamp examination of the eyes revealed corneal damage similar to that observed with excessive ultraviolet light exposure.

Dermatologic toxicity of cytosine arabinoside has not been reported with conventional doses; however, with high-dose cytosine arabinoside, skin toxicity appeared and was related to the duration of treatment. Patients developed a generalized erythematous maculopapular rash, often with intense painful erythema of the palms and soles, which was accompanied by bulla formation and desquamation in severe cases; symptoms began a median of 6 days after initiating therapy (range 2-7 days). For regimens of 4 days or less, skin toxicity was limited to a mild rash in 1 of 12 patients (Table 2). With the 6-day regimen, 7/27 patients (26%) were affected, and with the 8-day regimen, there was a further increase in frequency (8/12, 67%) as well as in severity (two grade 4) of skin toxicity (p < 0.02). Increasing the cytosine arabinoside dose rather than duration (4.5 g/sq m, 6 days) did not increase skin toxicity. Biopsies exhibited vacuolar degeneration of individual basal cells in the epidermis, dyskaratosis, and sparse lymphocyte infiltrate in the upper dermis.

Central nervous system (CNS) toxicity was dose-limiting and was not predicted by experience with cytosine arabinoside at conventional doses. A detailed description of the CNS toxicity has been reported separately.10 To summarize, cerebellar dysfunction predominated, with dysarthria, dysdiadochokinesia, and ataxia. A mild cognitive dysfunction, manifested by personality changes or impaired ability to perform calculations, accompanied the cerebellar findings in 3 of the 8 patients. The occurrence of CNS toxicity was not related to CNS leukemia, previous intrathecal therapy, cranial irradiation, or infection. Examination of spinal fluid and computerized x-ray tomography were performed at the onset of symptoms, but were normal in all cases. The symptoms began 6–8 days after initiating therapy, and in the absence of grade 4 toxicity, the dysfunction lasted 3–7 days. The CNS toxicity was primarily related to cytosine arabinoside dose rather than duration of therapy. It was not observed in the first 12 patients (2- and 4-day courses) and was present in 4/39 (10%) patients given the 6- and 8-day schedules. Two of these patients had severe (grade 3) toxicity, but none was fatal or irreversible. These findings are in sharp contrast to the outcome of patients receiving 6 days (12 doses) of 4.5 g/sq m, where 4 of 6 were affected (one grade 1, one grade 3, two grade 4). This increase in grade 4 cerebellar toxicity was significant compared to 3 g/sq m for 6 days (12 doses) regimen (p < 0.02). The CNS toxicity prohibited treatment of additional patients with 4.5 g/sq m for 6 days, and shorter treatment schedules at this dose were not examined.

Gastrointestinal toxicity of cytosine arabinoside included nausea and vomiting, diarrhea, and abnormalities in liver chemistries. Nausea and vomiting were generally more severe than observed with conventional doses of cytosine arabinoside, but bore no relation to duration or dose. Overall, nausea or vomiting occurred in 86% of patients; no patient had grade 4 toxicity and only 3 had grade 3. Diarrhea was related to both duration and dose of cytosine arabinoside. At 3 g/sq m for 2–6 days, 16 of 39 patients exhibited diarrhea, compared to 12 of 12 patients who received 8 days of cytosine arabinoside (p < 0.01). All of the patients treated with 4.5 g/sq m for 6 days (6/6, 100%) had diarrhea, with 4 patients having grade 3 toxicity. When compared to 3 g/sq m for 6 days, the frequency of diarrhea with 4.5 g/sq m for 6 days was significantly increased (p < 0.01), as was the severity (p < 0.05). None of the patients had grade 4 toxicity. Abnormal liver chemistries (bilirubin, alkaline phosphatase, and transaminases), were observed in most patients, with mild-to-moderate involvement occurring in 43/57 (75%) patients. Severe (grade 3) toxicity occurred only at the highest dose and duration evaluated. No grade 4 liver toxicity was encountered.

In summary, side effects related to the duration of

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**Table 2. Frequency of Systemic Effects of High-Dose Cytosine Arabinoside**

<table>
<thead>
<tr>
<th>Dose Level (g/sq m q. 12 hr x No. Doses)</th>
<th>Number of Patients</th>
<th>Percent With Toxicity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Skin</td>
<td>CNS</td>
</tr>
<tr>
<td>3 × 4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3 × 8</td>
<td>10</td>
<td>2(0)</td>
</tr>
<tr>
<td>3 × 12</td>
<td>27</td>
<td>37(0)</td>
</tr>
<tr>
<td>3 × 16</td>
<td>12</td>
<td>100(0)</td>
</tr>
<tr>
<td>4.5 × 12</td>
<td>6</td>
<td>50(0)</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>47(0)</td>
</tr>
</tbody>
</table>
therapy included conjunctivitis/photophobia, skin rash, diarrhea, and liver dysfunction, so that the maximum tolerated duration was 12 doses (6 days). Toxicity related to higher dose (i.e., 3 g/sq m versus 4.5 g/sq m) was seen in the central nervous system (cerebellar) and gastrointestinal system (diarrhea). The maximum tolerated combination of duration and dose was therefore determined to be 3 g/sq m every 12 hr for 6 days (12 doses).

Hematologic Effects

Aplasia of the bone marrow developed in nearly all patients. Eleven patients died while aplastic within 3 wk of initiating therapy and were not evaluable for determining time to recovery of bone marrow; the 17 patients who failed to achieve remission were also excluded from the analysis of bone marrow recovery. Twenty-nine patients (21 with complete remissions, 8 with partial remissions) recovered normal peripheral blood counts. Recovery was not delayed by increased duration or dose of cytosine arabinoside. The median time to recovery of granulocytes (>500/µl) was 28 days (range 22–40 days) from initiating therapy. Platelet recovery (>20,000/µl, without platelet transfusion) occurred in a median of 25 days (range 16–41 days). Fever during the period of granulocytopenia was nearly universal, and in approximately half of the patients, a documented infection was found. Fatal infections occurred in 16% of the patients. Fever due to cytosine arabinoside (drug fever) has been reported, and some of the fevers may not have been infectious in origin. Severe hemorrhage, due to thrombocytopenia, occurred in 10% of the patients, and 3% were fatal.

Antileukemic Effects

A comparison of the effectiveness of the various high-dose cytosine arabinoside schedules is found in Table 3. Eleven patients who died with aplasia, without evidence of leukemia, before day 21 were not considered evaluable for antileukemic response. While partial remissions are not usually of clinical importance in patients with acute leukemia, with the stringent criteria used, the 8 patients who achieved partial remission had unmaintained responses of similar duration to the 21 patients with complete remission. As the duration of therapy was increased, there was improved antileukemic effect. Only 2 of 11 patients achieved complete remissions with the 2- and 4-day regimens, compared to 16 of 29 treated for 6–8 days ($p < 0.05$). Increasing the dose to 4.5 g/sq m resulted in no further improvement in response rate, although only 6 patients were evaluable at this higher dose.

A clearer relationship between duration of treatment and response can be seen in the 37 evaluable patients with acute nonlymphoblastic leukemia (Table 4). There is a significantly increased complete remission rate for 6- and 8-day regimens (17 of 28) compared to the 2- and 4-day schedules (2 of 9), $p < 0.05$. The duration of unmaintained response for the 22 acute nonlymphoblastic leukemia patients who achieved a remission with 6–8-day schedules is depicted in Fig. 1 as a Kaplan-Meier plot. These data were combined, since there was no apparent difference in the length of remissions for the two regimens. The similarity in duration of remission between the complete and partial remission patients can be appreciated. Of note is the fact that although the median is relatively short (4 mo), after that time the relapse rate appears to decrease, so that approximately 20% of patients have unmaintained remissions of more than 1-yr duration.

Too few patients with other leukemias were treated to establish a valid response rate. Two of 4 patients with acute lymphoblastic leukemia (3 evaluable) responded, with 1 patient achieving a complete remission. Seven patients with chronic myelogenous leukemia in accelerated phase (6 evaluable) were treated, with only 1 complete remission (normal peripheral blood counts, normal bone marrow with normal cytogenetics, and loss of the Philadelphia chromosome). All of the 3 responding patients had received 6–8-day regimens.

The response to high-dose cytosine arabinoside was influenced by previous therapy. Analysis of the 36 patients surviving >3 wk.

Table 3. Antileukemic Effect of High-Dose Cytosine Arabinoside

<table>
<thead>
<tr>
<th>Dose Level (g/sq m)</th>
<th>Number of Patients</th>
<th>Number of Evaluable Patients</th>
<th>Remissions†</th>
<th>Duration of Unmaintained Response‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 x 4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3(1–7)</td>
</tr>
<tr>
<td>3 x 8</td>
<td>10</td>
<td>9</td>
<td>2(22)</td>
<td>0</td>
</tr>
<tr>
<td>3 x 12</td>
<td>27</td>
<td>21</td>
<td>12(57)</td>
<td>4(2–21)</td>
</tr>
<tr>
<td>3 x 16</td>
<td>12</td>
<td>8</td>
<td>4(50)</td>
<td>3(13)</td>
</tr>
<tr>
<td>4.5 x 12</td>
<td>6</td>
<td>6</td>
<td>3(50)</td>
<td>2.5(2–3)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate percent of evaluable patients.
†Median duration in months; range in brackets.
patients with acute nonlymphoblastic leukemia receiving schedules including at least 12 doses (6–8 days) is presented in Table 5. Thirty-five of 36 had received cytosine arabinoside previously in conventional doses; 14 were considered to be resistant, having failed one or more courses of conventional dose cytosine arabinoside just before treatment with a high-dose regimen. For the 22 patients without documented resistance to cytosine arabinoside, there were 5 early deaths, and a complete remission was achieved in 15 of 17 evaluable patients (88%); 2 patients had partial remissions. Sixteen of the patients were undergoing their first reinduction attempt. For this particularly favorable group, there was 1 early death, 14 (93%) had a complete remission, and 1 (7%) had a partial remission. In contrast, for the 11 evaluable patients in the resistant group, only 2 patients (18%) had a complete remission and 3 (27%) had a partial remission. There were significantly more complete remissions in nonresistant patients (15/17) compared to those patients with documented resistance (2/11), \( p < 0.001 \). There was no difference in the duration of unmaintained response for the two groups of patients (median 4 mo, range 2–26 + mo).

### DISCUSSION

Cytosine arabinoside has been the mainstay in primary treatment regimens for acute nonlymphoblastic leukemia for over a decade.\(^1\)\(^7\) In combination with an anthracycline antibiotic, initial induction regimens typically result in 60%–80% complete remissions.\(^12\)\(^14\) The treatment of acute leukemia in relapse (second and subsequent remission induction) remains a more difficult problem, as only one-quarter of patients achieve additional remissions with the best new agents available.\(^15\)\(^22\) Since there is a substantial body of evidence supporting the concept that higher concentrations of antitumor therapy can increase response rates,\(^23\) we undertook to determine whether high-dose cytosine arabinoside would be more effective than conventional regimens.

The usual schedule of cytosine arabinoside employs either a continuous infusion of 100 mg/sq m/day or bolus doses of 100 mg/sq m every 12 hr for 7–10 days. The two regimens appear to be equivalent both in toxicity and antileukemic effect. Experience with higher doses of cytosine arabinoside is limited. Early clinical studies explored a variety of cytosine arabinoside schedules to determine toxicity and tumor re-
sponse. Single intravenous bolus doses up to 4.2 g/sq m were given without toxicity. This apparent lack of toxicity is felt to be a consequence of the rapid inactivation of cytosine arabinoside in vivo, which limits the number of cells susceptible to killing by this cell-cycle-specific drug. The predicted increase in toxicity from prolonged exposure to effective concentrations of cytosine arabinoside also has been confirmed in clinical studies. For example, a bolus of 600 mg/sq m produced no myelosuppression, while the same dose administered as a 24-hr or 48-hr infusion resulted in progressively greater myelosuppression. Similarly, cytosine arabinoside given at a dose of 30 mg/sq m/day required 25 days of treatment to produce bone marrow hypocellularity as a 4-hr infusion, but required only 10 days to achieve the same marrow effect as a daily 12-hr infusion. Based on these observations, cytosine arabinoside toxicity to proliferating tissues (e.g., gastrointestinal mucosa) should be influenced primarily by duration of drug exposure rather than peak drug concentrations. Thus, large bolus doses might be tolerated without significantly increased toxicity, while therapeutic effectiveness would be increased if the resistance of tumor cells were overcome by higher peak concentrations. Recently, Rudnick and coworkers showed that single doses of cytosine arabinoside, as high as 7.5 g/sq m (75 times the conventional dose), could be given without lethal toxicity, and one patient with refractory leukemia achieved complete remission after receiving 3 g/sq m every 12 hr for 2 days. With this dose as a starting point, we have systematically determined the maximum tolerated dose and duration of cytosine arabinoside given by 1-hr intravenous infusion at 12-hr intervals.

The maximum duration of treatment was found to be 6 days, due to severe diarrhea and skin reactions in patients treated for 8 days. Nausea, vomiting, and abnormalities in liver chemistries also were more severe than with conventional cytosine arabinoside regimens, but were not dose-limiting. The maximum cytosine arabinoside dose was limited to 3 g/sq m by the occurrence of severe CNS toxicity at 4.5 g/sq m. The CNS toxicity of high-dose cytosine arabinoside was primarily manifest by cerebellar dysfunction, although 3 of 8 affected individuals had concomitant mild cerebral signs (personality changes or drowsiness). The pathologic changes in the cerebellum consisted of loss of Purkinje cells from lateral hemispheres, with Bergmann glia proliferation. Cerebrospinal fluid concentrations of cytosine arabinoside can reach 40%–60% of plasma levels during continuous intravenous cytosine arabinoside infusion. Early and coworkers have demonstrated a similar high CNS level with high-dose bolus cytosine arabinoside. Despite the penetration into the CNS, little neurologic toxicity has been attributed to cytosine arabinoside. The only neurologic problems reported in two other studies using high-dose cytosine arabinoside were transient somnolence or confusion which were associated with rapid (less than 1 hr) infusions. Of interest, similar cerebellar toxicity is occasionally seen with another pyrimidine analog, 5-fluorouracil. The CNS penetration of high-dose cytosine arabinoside may make effective prophylaxis or treatment of meningeal leukemia possible with systemic therapy.

Other organ systems exhibiting toxicity to high-dose cytosine arabinoside that are not commonly affected by conventional doses include the skin and the eye. Skin changes rarely have been reported with cytosine arabinoside. We observed an unusual and dramatic palmar and plantar erythema, accompanied by bulla formation in severe cases. The clinical and pathologic picture was similar to graft-versus-host disease and the toxic epidermal necrolysis seen in bone marrow transplantation. The incidence of skin toxicity was related to both dose and duration of treatment. The severity was primarily related to duration, since severe skin reactions only occurred in patients treated for 8 days. Painful palms and soles in the more severe cases appeared to respond to a brief course of glucocorticoid treatment.

 Conjunctivitis with photophobia was a troublesome complaint that occurred in 85% of patients who did not receive prophylactic glucocorticoid eye drops and 16% of patients who did receive eye drops. The mechanism by which the glucocorticoid eye drops prevented con-

### Table 5. Relationship of Response of Acute Nonlymphoblastic Leukemia and Resistance to Conventional Dose Cytosine Arabinoside

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients*</th>
<th>Number of Evaluable Patients†</th>
<th>Remissions‡</th>
<th>Response§ Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresistant</td>
<td>22</td>
<td>17</td>
<td>15(88)</td>
<td>77</td>
</tr>
<tr>
<td>Resistant</td>
<td>14</td>
<td>11</td>
<td>2(18)</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>28</td>
<td>17(61)</td>
<td>61</td>
</tr>
</tbody>
</table>

*Patients receiving ≥ 12 doses (6–8 day) schedules.†Number surviving > 21 days.‡Numbers in parentheses indicate percent of evaluable patients.§Response rate for all patients entered on study = Complete + partial remissions/Number of patients treated × 100.
Junctivitis is not known, but the use of nonsteroidal eye drops was ineffective. Failure to adhere to a rigorous 6–8 hourly schedule appeared to be responsible for some episodes of conjunctivitis among patients who received eye drops. Corneal toxicity from topical cytosine arabinoside has been described, and it can be prevented by concomitant deoxycytidine triphosphate drops. Thus, the toxicity of high-dose systemic cytosine arabinoside is probably a direct effect on corneal epithelium by cytosine arabinoside (or its metabolites) present in the tears. Other reports of conjunctivitis due to high-dose cytosine arabinoside have appeared.

The antileukemic effectiveness of high-dose cytosine arabinoside was related to duration of treatment. A significantly greater proportion of patients treated with regimens of at least 6 days duration (12 or more doses) achieved complete remissions than did patients who received 2–4 days of treatment. Comparison of the 6- and 8-day regimens revealed no apparent difference in response rate, but the longer treatment was substantially more toxic. The CNS toxicity of cytosine arabinoside precluded determination of any possible dose effect for doses above 3 g/sq m. Using the maximally tolerated regimen of 3 g/sq m every 12 hr for 6 days (12 doses), complete remissions were obtained in 12 of all 27 patients (44%) with refractory acute leukemia. Considering only the 24 patients with acute nonlymphoblastic leukemia, complete responses were obtained in 12 (50%); if patients surviving less than 3 wk are excluded, the complete response rate is 12/19 (60%). Thus, high-dose cytosine arabinoside is superior to the best two new agents, m-AMSA and 5-azacytidine, which result in a complete response rate of less than 25% in similar groups of patients.

Our results also provide evidence that high-dose cytosine arabinoside is more active than conventional doses. Unfortunately, there is little information available on the response of previously treated patients to conventional doses of cytosine arabinoside used as a single agent. In two recent studies, using combinations of conventional doses of cytosine arabinoside and anthracyclines, patients with acute nonlymphoblastic leukemia in their first relapse had complete remission rates of 73% (8 of 11 patients) and 67% (12 of 18 patients). Using high-dose cytosine arabinoside alone, we obtained similar results for this favorable group of patients, with 14 of 15 patients (93%) achieving a complete remission. Perhaps more convincing are the responses of patients with demonstrated resistance to cytosine arabinoside. These 14 patients had failed one or more induction attempts with conventional doses before receiving high-dose cytosine arabinoside. Complete remissions were achieved in 2 of 11 evaluable patients, and partial remissions in another 3 patients, for a total response rate of 45% (5/11). Finally, although no patient received maintenance therapy, 4 of the 22 responders remained in complete remission in excess of 1 yr. In each of these patients, the duration of this unmaintained response was at least twice their initial remission duration obtained with conventional doses of cytosine arabinoside.

Insufficient numbers of patients with leukemia (other than acute nonlymphoblastic leukemia) were treated to determine the activity of high-dose cytosine arabinoside; however, there may be activity in acute lymphoblastic leukemia, with 2 of 3 evaluable patients responding (one complete remission). Early and colleagues reported 4 of 6 patients with acute lymphoblastic leukemia responding, but without any complete remissions. Chronic myelogenous leukemia in accelerated phase holds less promise for response, with only 1 brief (2 mo) complete response in 6 evaluable patients.

In summary, the maximum dose and duration of high-dose cytosine arabinoside was found to be 3 g/sq m every 12 hr for 12 doses. Further dose escalation was prevented by nonmyeloid toxicity involving the eye, skin, gastrointestinal system (liver and diarrhea), and the CNS (cerebellum). Used at the maximum tolerated dose, cytosine arabinoside has striking activity against refractory acute leukemia. Half of the patients with acute nonlymphoblastic leukemia entered complete remission, including 20% of patients unresponsive to conventional doses of cytosine arabinoside and more than 90% of patients in their first relapse. Unmaintained remissions lasting more than 1 yr were obtained in 20% of the responding patients.

It is possible that high-dose cytosine arabinoside used in the primary treatment of acute nonlymphoblastic leukemia (remission induction or consolidation) would result in an improved remission rate or prolonged remission duration; however, the possibility of serious CNS toxicity dictates that caution be used with this approach. Also of importance will be studies to determine the activity of high-dose cytosine arabinoside in combination with other agents in the treatment of refractory leukemia. Preliminary results with combination therapy have shown high-dose cytosine arabinoside with anthracyclines, m-AMSA, and L-asparaginase to be active in patients with relapsed acute leukemia, more patients will be required to conclude a beneficial effect of the combinations in specific subgroups. For example, the anthracycline combinations appear to have improved activity in patients with acute nonlymphoblastic leukemia with...
documented resistance to cytosine arabinoside in conventional doses. Finally, although cytosine arabinoside has not demonstrated activity against solid tumors, it would be of interest to determine whether the high-dose regimen can overcome de novo resistance in this setting. A recent report demonstrated a brief (13–76 days) tumor response in 3 refractory lymphoma patients.

ACKNOWLEDGMENT

The authors gratefully acknowledge the support from George Royer, M.D., and the Upjohn Company.

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High-dose cytosine arabinoside therapy for refractory leukemia

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