Dose Schedule and Antitumor Studies of Arabinosyl Cytosine (NSC 63878)\textsuperscript{6,7}

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SUMMARY

The effect of dose and schedule of arabinosyl cytosine (ara-C) on bone marrow function and antitumor response was evaluated in 88 patients with metastatic cancer. It was found that: (a) Single doses of ara-C produced no myelosuppressive or antitumor effect. (b) Continuous infusion for 48 or 96 hours resulted in a steep dose-response curve with respect to marrow depression; 18–38\% of analyzable patients had tumor regression. (c) Continuous infusion for 24 hours produced an increase in marrow depression with doses up to 1200 mg/sq m, after which further increase in dose did not produce greater myelosuppression. Tumor regression occurred in 10\% of these patients. The above dose-marrow response curves, interpreted with a background of experimental data, suggest that a substantial nonproliferating marrow stem cell pool exists in man. (d) Granulocytopenia was more frequent than thrombocytopenia, and lymphopenia did not occur. Platelet "rebound" to greater than 1,000,000 per cu mm following myelosuppression was common. The cell kinetic and therapeutic implications of these observations are discussed.

INTRODUCTION

Arabinosyl cytosine (1-ß-D-arabinofuranosylcytosine) (ara-C) is a pyrimidine nucleoside analog which selectively interferes with DNA synthesis (9, 30). It is cytotoxic to mammalian cells in culture and is active \textit{in vitro} and \textit{in vivo} against a variety of DNA viruses (35, 9, 26, 30, 39). It has potent antitumor activity in a variety of transplanted tumor systems (13, 16, 17, 31, 41) and has definite but limited effectiveness in the treatment of acute leukemia and lymphoma in man (15, 22, 24, 38, 43).

ara-C, in common with other agents that affect cells only during a specific stage of the mitotic cycle, affects proliferating cells but not nonproliferating cells. Quantitative studies of the dose and schedule of such agents on the normal bone marrow and lymphoma cells in the mouse resulted in different dose-response curves than occur with, for example, alkylating agents. By appropriate selection of the dose schedule of ara-C, a markedly superior tumor therapeutic index can be attained in experimental systems (see Discussion and Refs. 4, 5, 36, 42).

The purpose of the present study is to define the effect of dose and schedule of ara-C on the normal bone marrow function and kinetics in man. The antitumor effect of ara-C was also evaluated. It was found that the dose schedule of ara-C markedly influences host tolerance in a quantitative and possibly qualitative manner. The results are consistent with generation times of replicating marrow cells of less than 48 hours and a substantial pool of nonproliferating marrow stem cells. Sixteen percent of the patients with measurable tumors had objective response.
MATERIALS AND METHODS

This study was performed by the Southwest Cancer Chemotherapy Study Group. Patients with metastatic carcinoma who had received conventional treatment previously were selected for study. Requisites for admission to the study included normal white blood and platelet counts and no myelosuppressive treatment during the preceding month. Patients with extensive prior X-irradiation were excluded from the study. The therapeutic potential and possible toxicity were explained to the patient and informed consent was obtained prior to the initiation of therapy.

The white blood count, differential, platelet count, hemoglobin, and reticulocyte count were obtained prior to treatment with ara-C and at least twice weekly during the study. Serum alkaline phosphatase, transaminases (SGOT and SGPT), bilirubin, blood urea nitrogen, and uric acid were measured prior to the study and at appropriate intervals during the study. On selected patients more definitive studies were performed, including electron microscopic examination of the bone marrow and oral mucosa and cell kinetic studies of the tumor and bone marrow during the period of treatment and recovery. The results of those studies are reported separately (1).

Patients selected for study were allocated randomly to four schedules of drug administration: single rapid intravenous injection (push); 24-hour continuous infusion; 48-hour continuous infusion; and 96-hour continuous infusion.

In addition, patients were assigned randomly to one of several initial dose levels within each of the four schedules. At any one time, this involved two or three dose levels within each schedule, and these levels were progressively increased for subsequent patients until the tolerated dose and dose-response curve was defined. The dose of ara-C per course (regardless of duration) is given in mg per sq m of body surface. The ara-C was diluted in five percent dextrose for intravenous administration. For the 48- and 96-hour infusions, material was made up for each 24-hour infusion. The stability of ara-C under such circumstances has been demonstrated. Drug was administered intravenously by constant, gravity flow, intravenous drip. Appropriate adjustments were made during the first several hours of infusion to assure relatively constant administration. The ara-C treatment was repeated at two-week intervals for a minimum of three treatments. Subsequent doses were at the next higher dose level for patients with little or no marrow toxicity. Otherwise, the dose was given at the same level or at reduced levels. Patients whose tumors responded continued to receive treatment courses until relapse occurred.

For patients with radiographically demonstrable or palpable tumors, measurements were made and recorded at one- to two-week intervals during the study. A significant objective response was defined as >50 percent reduction in area of measured tumors. The duration of response was the time from onset of response until unequivocal evidence for relapse.

RESULTS

Thirteen institutions in the Southwest Cancer Chemotherapy Study Group participated in this study. A total of 112 patients were entered into the study of whom 88 were acceptable for analysis. The institutions and number of acceptable patients are as follows: Baylor University College of Medicine, 8; Cleveland Clinic, 6; The University of Texas Southwestern Medical School at Dallas, 1; Henry Ford Hospital, 8; The University of Texas Medical Branch at Galveston, 2; Wilford Hall USAF Hospital, Lackland Air Force Base, 2; Louisiana State University School of Medicine, 12; The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 33; Northwestern University School of Medicine, 4; Scott and White Clinic, 6; Tulane University School of Medicine, 3; Veterans Administration Research Hospital in Chicago, 1; Washington University School of Medicine, 2. Twenty-four patients were excluded from the study because: (a) they did not fit the criteria for selection; (b) the protocol was not followed; and/or (c) the patients were lost to follow-up during the study.

The distribution of patients by type of malignancy is presented in Table 1. Response will be considered below.

Nausea and vomiting during drug administration occurred in two-thirds of the patients but was severe in only eight patients. It tended to subside spontaneously during ara-C infusion. Recovery following cessation of drug administration occurred rapidly and completely. In general, nausea and vomiting were dose related for a given schedule but tended to be less per given total dose for the longer duration of infusions.

Hepatotoxicity, in terms of increase in transaminases and alkaline phosphatase, occurred in 16 patients. Such increases were transient, and values returned to normal within two weeks following cessation of ara-C administration. In no instance did jaundice or progressive hepatic failure develop. Autopsies were performed and analyzed in 21 of the patients, and liver disease attributable to ara-C was not observed.

The major and dose-limiting toxicity of ara-C was bone marrow depression. In view of the cell kinetic factors and the effect of the schedule of ara-C administration on the antitumor index in experimental systems, the influence of the various schedules of ara-C employed in this study on bone marrow function were analyzed in detail.

Bone marrow depression was quantitatively evaluated and scored (Table 2). Mild white count or platelet depression was given a score of 1, and more severe depression was given a score of 2. These were totaled for a given number of trials, and the marrow depression score was the number divided by the number of trials (Table 2).

To determine whether prior administration of ara-C modified subsequent tolerance to this agent, the marrow toxicity scores were compared for the first, second, and third or subsequent course of ara-C. The comparisons were made within the same schedule and dose level. While there was some variation, there was not consistently more or less marrow toxicity for the initial course as compared to subsequent courses of treatment. It was concluded that prior administration of ara-C did not affect subsequent tolerance to this agent provided at least two weeks had elapsed. Because of this, the trials for the various courses of treatment were pooled in the following analysis of bone marrow function.

The effect of various doses and schedules on ara-C administration on white cell and platelet depression is presented in Table 3 and Chart 1. With single intravenous injections (push),
Table 1

<table>
<thead>
<tr>
<th>Disease category</th>
<th>No. of cases which could be evaluated for</th>
<th>Tumor response</th>
<th>No.</th>
<th>Extent*</th>
<th>Duration (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hematology</td>
<td>Tumor response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>23</td>
<td>13</td>
<td>0</td>
<td>70% decrease in size of liver and pelvic mass</td>
<td>4</td>
</tr>
<tr>
<td>Adenocarcinoma of colon</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>70% decrease in mass of lung and pelvic mass</td>
<td>9+</td>
</tr>
<tr>
<td>Carcinoma, primary unknown</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>80% decrease in mass above knee</td>
<td>3</td>
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<tr>
<td>Osteogenic and soft tissue sarcoma</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>50%, 90%, 60%</td>
<td>6, 3, 3</td>
</tr>
<tr>
<td>Carcinoma of stomach</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Carcinoma of cervix uteri</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma of oral cavity</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>4</td>
<td>3</td>
<td>0</td>
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<td></td>
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<tr>
<td>Childhood solid tumors</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
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<td>Carcinoma of kidney</td>
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<td>Carcinoma of ovary</td>
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<td>0</td>
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<td></td>
</tr>
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<td>Carcinoma of vulva</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma of esophagus</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>70% decrease in size of mediastinal mass and nodes</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>88</td>
<td>44</td>
<td>7 (16%)</td>
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<td></td>
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</table>

*% decrease in size of measurable lesions.

Table 2

<table>
<thead>
<tr>
<th>Marrow depression</th>
<th>Value</th>
<th>Marrow depression score = Sum of WBC and platelet value / Number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC nadir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5 x 10⁴</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;3 x 10³</td>
<td>2</td>
<td></td>
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<tr>
<td>Platelet nadir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–200 x 10⁴</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;50 x 10³</td>
<td>2</td>
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</tr>
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</table>

Marrow depression score = (Sum of WBC and platelet value) / Number of trials

Mild platelet depression followed one trial at 1200 mg/sq m. Otherwise, no bone marrow toxicity was observed at doses as high as 4200 mg/sq m. It was concluded that very large single doses of ara-C at two-week intervals were not myelosuppressive. With 24-hour continuous infusions, white cell and platelet depression began to appear at doses of 600 mg/sq m, and there was increasing myelosuppression through doses of 1500 mg/sq m. From dose levels of 1500 mg/sq m through doses of 3200 mg/sq m, myelosuppression occurred regularly but did not increase in amount.

With 48-hour infusions of ara-C significant white count and platelet depression began to appear at 450 mg/sq m, progressively increased with increasing doses, and was dose limiting at approximately 1000 mg/sq m. Similarly, with 96-hour infusions white cell and platelet depression was evident at 400 mg/sq m and progressively increased to be dose-limiting after 800 mg/sq m. Thus, the dose response curves for the 48-hour and 96-hour infusions were steep and similar (Chart 1). For these schedules, a given dose produces the same degree of toxicity whether given over a 48- or a 96-hour period (see Discussion). The dose-response curve for the 24-hour infusion of ara-C is steep over a short range, perhaps 600 to 1500 mg/sq m, but then plateaus at doses above this level (see Discussion).

Reticulocyte counts were obtained every two to three days in 113 of the ara-C trials (Table 3). Significant reticulocytopenia was defined as two or more values of less than 0.1 percent in patients in whom the pretreatment value was greater than 0.5 percent. The reticulocyte count for the 20 patients with significant reticulocytopenia who received 24-hour ara-C infusions are presented in Chart 2. Reticulocytopenia was in progress by two or three days and was maximal from three to nine days; recovery was underway by the eleventh to twelfth day. Reticulocytopenia did not occur regularly with any dose given as a single injection (push). For the 48- and 96-hour infusions, reticulocytopenia occurred regularly at all dose levels. For 24-hour infusions, reticulocytopenia occurred infrequently at doses below 900 mg/sq m; it occurred in approximately half the trials from 900 through 1200 mg/sq m and regularly at higher doses. In general, reticulocytopenia occurred at much lower doses than that required to produce white count or platelet depression.

The relative effect on peripheral white blood cell and platelet depression by ara-C is presented in Table 4. White count depression was approximately twice as frequent and severe as platelet depression. In the 39 trials in which thrombocytopenia occurred, 16 were followed by "rebound" thrombocytosis to greater than 1,000,000 platelets per cu mm.

The white blood cell nadir occurred between the eighth and twentieth days and tended to be later following the 48- and
Table 3

<table>
<thead>
<tr>
<th>Dose (mg/sq m)</th>
<th>WBC &amp; platelet effect</th>
<th>24 hr</th>
<th>WBC &amp; platelet effect</th>
<th>Reticulocytopenia</th>
<th>48 hr</th>
<th>WBC &amp; platelet effect</th>
<th>Reticulocytopenia</th>
<th>96 hr</th>
<th>WBC &amp; platelet effect</th>
<th>Reticulocytopenia</th>
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<td>200</td>
<td>0/5</td>
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<td>1/3</td>
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<td>300</td>
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<td>7/9</td>
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<td>3/3</td>
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</tbody>
</table>

Effect of dose and schedule of cytosine arabinoside on the bone marrow.

*See Table 2.

No. with significant decrease in reticulocyte count/no, with reticulocyte counts at least twice weekly.

96-hour infusion than following the 24-hour infusion. This was probably not a function of the schedule but rather the degree of white count depression. Thus, there was good correlation between the magnitude of white count depression for a given trial and the time to white count nadir.

The relative effect of ara-C on the blood granulocyte and lymphocyte count is presented in Chart 3. The 20 patients who had two or more white counts of less than 2000/cu mm following ara-C, and who had white blood cell and differential counts at least two times weekly, were selected. It is apparent that the white count depression resulting from ara-C was entirely due to granulocytopenia. A significant change in the absolute lymphocyte count did not occur.

The antitumor effects of ara-C are considered in Table 1. In order to be considered for antitumor response, the patient must have had measurable disease and have received at least two courses of ara-C administration. Forty-four of the 88 patients qualified, and, of these, seven (16 percent) had an antitumor effect. The responses by drug schedule were as fol-
Table 4

<table>
<thead>
<tr>
<th>Schedule</th>
<th>No. of trials</th>
<th>White count depression</th>
<th>Platelet depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total (nadir &gt; 5,000)</td>
<td>3,000–5,000</td>
</tr>
<tr>
<td>Push</td>
<td>51</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>24 hr</td>
<td>83</td>
<td>26</td>
<td>16</td>
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<tr>
<td>48 hr</td>
<td>52</td>
<td>28</td>
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</tr>
<tr>
<td>96 hr</td>
<td>36</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>222</td>
<td>66</td>
<td>35</td>
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</table>

Relative frequency of white cell count and platelet depression.

DISCUSSION

In experimental systems, the biologic activity of ara-C is markedly dependent upon the schedule of drug administration. Employing the spleen colony-forming unit technic in mice, Bruce has studied the relative effects of various antitumor agents on the normal bone marrow "stem cell" (4, 5, 42). With cycle-active agents (agents which affect only proliferating cells), a progressive decrease in surviving bone marrow stem cells to 20 percent of the control level occurs with increasing dose (given over a 24-hour period). With further increase in dose, no further increase in marrow stem cell destruction occurs since these 20 percent of the cells are nonproliferating. With destruction of the proliferating cells, these nonproliferating cells presumably reenter the proliferating pool. Thus, the dose response curve "plateaus" for cycle-active agents. This does not occur with alkylating agents or other noncycle-active agents. In the same system over 99.9 percent of AKR lymphoma cells are destroyed because of their short generation time (12 hours) and the fact that almost all of the cells are proliferating. This knowledge of the biologic action of antitumor agents and the kinetics of the bone marrow and tumor cells has allowed for appropriate exploitation in terms of dose and schedule of administration, and thus an improved therapeutic index in experimental systems. For example, Skipper et al. have demonstrated that, for equally toxic doses, daily ara-C administration will produce an 80 percent increase in median survival of L1210 mouse leukemia, whereas continuous administration for 24 hours every four days will effect cure in the majority of animals. It is essentially the above experimental data that prompted the present study.

ara-C is an ideal agent for the extension of such studies to man. It is a cycle-active agent affecting cells only during the DNA synthesis phase (S-phase) of the mitotic cycle (8, 9, 30, 34). Moreover, it affects only the bone marrow replicating cells in man and does not produce comparable damage to the gastrointestinal tract (22, 24, 38). Finally, ara-C is metabolized rapidly in man, and its biochemical effects are quickly reversed (11). This contrasts with certain other antimetabolites as, for example, Methotrexate (23). Thus, the biochemical effect of ara-C is reversed quickly following cessation of administration of the drug.

Cell kinetic studies of the human bone marrow indicate that the generation time for replicating cells ranges from 12 to 30 hours. The shorter generation times apply primarily to erythroid precursors and the immature myeloid cells (myeloblasts) (12, 27–29, 32).
Because of these considerations, dose response curves were performed with ara-C for the following schedules: single intravenous injection; 24-hour infusion; 48-hour infusion; and 96-hour infusion. If the above data and assumptions are correct, a single intravenous injection should produce little or no myelosuppression. Thus, perhaps 50 percent of the cells with a 12-hour generation time would be synthesizing DNA. At any given time period, a brief exposure to ara-C could, at best, damage half the cells. On the other hand, the 48- and 96-hour infusions of drug administration should result in exposure during the S-phase (DNA synthesis) of all replicating marrow stem cells, assuming that the generation time of proliferating cells is less than 48 hours. The dose response curve for both of these schedules was linear and steep so that, with progressive increase in dose, there was progressive impairment of granulocyte and platelet production. Failure to see a "plateau" with these two schedules can be attributed to drug effect on cells moving from the nonproliferating pool to the proliferating pool as well as on the proliferating pool. It is of interest that for the 48- and 96-hour infusions, the same dose produced essentially the same degree of myelosuppression.

The type of dose response curve for the 24-hour infusion of ara-C has not been observed in clinical trials of other cancer chemotherapeutic agents. Thus, with increasing doses up to 1500 mg/sq m, there is increasing depression of granulocyte and platelet production, after which there is no further increase in myelosuppression up to doses of 3200 mg/sq m. This "plateauing" of the dose-response curve is similar to that observed on bone marrow stem cells in mice with cell cycle-active agents (4, 5, 42). One exception for this curve in mice is that a proportion of the marrow stem cells are in a nonproliferating state. Such cells are not damaged by cycle-active agents and presumably reenter the proliferating pool. Another explanation is that a proportion of the stem cells have generation times of greater than 24 hours and thus survive a 24-hour exposure to a cycle-active agent. In summary, the above data are consistent with the interpretation that the generation time of replicating marrow granulocyte and platelet precursors is less than 48 hours and that a proportion of such cells is in the nonproliferating pool.

Other clinical studies of the effect of dose and schedule of ara-C have produced results generally consistent with the above (6, 14). One exception is the observation by Burke et al. (6) wherein plateauing of the dose-response curve for five-day infusions appeared to occur at doses in excess of 350 mg/sq m.

For a given dose of ara-C, reticulocytopenia occurred more frequently and thrombocytopenia less frequently than granulocytopenia (Tables 3, 4). Studies of the bone marrow in patients receiving cycle-active chemotherapeutic agents indicate that, in general, erythropoiesis is affected more than granulocytopoiesis (2, 18, 40). This is perhaps due to the shorter generation time of erythroid precursors as compared to granulocytic precursors (12, 27, 28, 32). This observation suggests that the acute myelosuppression following cycle-active agents does not result primarily from damage to a totipotential stem cell since such an effect should produce comparable depression of all three elements. Such an effect is more consistent with a differential effect on primordial cells already committed to hematopoiesis.

While platelet rebound has been described following the administration of other myelosuppressive agents, particularly cycle-active agents such as Methotrexate, it has not been reported with the high frequency that followed ara-C in the present studies. This is perhaps due to the relatively brief biochemical and pharmacologic insult delivered by ara-C as compared with a more prolonged effect of the irreversibly bound drugs such as alkylating agents and for Methotrexate which remains bound to the target enzyme for prolonged periods of time (11, 23).

ara-C will depress primary immune response but not secondary immune response in experimental systems and probably in man (7, 21, 25). Many of the immunosuppressive agents, such as X-irradiation and the alkylating agents, produce a rapid decrease in circulating lymphocytes. This was not observed to be the case for ara-C in man (Chart 3). This is perhaps explained by the fact that the lymphocytes constitute a large body of recirculating cells which, under normal circumstances, have a slow turnover (20). The small circulating lymphocytes do not incorporate tritiated thymidine following flash exposure and thus are not synthesizing DNA and would not be expected to be adversely affected by ara-C. Why then does ara-C depress immune response? The primary immune response involves processing of the antigen by macrophages for delivery to small lymphocytes which transform into large lymphocytes and rapidly proliferate. Thus, as has been demonstrated in experimental systems, it is the proliferative phase of the immune response which is adversely affected by ara-C (21).

ara-C is an effective agent for the treatment of acute leukemia in man (15, 22, 24, 43). Recently, it has been demonstrated that with continuous five-day, ara-C administration, 40 to 50 percent of adults with acute myelocytic leukemia achieve complete remission (3). This study was based on the evidence that the generation time for acute myelocytic leukemic cells averages three to four days, and a five-day course would thus have the opportunity of destroying all proliferating cells (10).

Relatively little is known of the kinetics of solid tumors in man. The doubling time would suggest a long generation time, but it is probable that a large proportion of the cells are in the nonproliferating pool and that the few proliferating cells have a fairly rapid turnover (19, 33).

Consistent with this is the fact that tumor response occurred in 7 of 44 patients in the present study and tended to be more frequent with the longer duration of treatment at higher doses. While this response rate and the reported response rate in solid tumors (37) is not particularly impressive, two extensions of the study seem indicated. One is the use of 24-hour infusions at intervals shorter than two weeks. Such infusions at four-day intervals are optimal in experimental systems (36). The second is the use of continuous infusion for 8–10 days, particularly in patients with adenocarcinoma of the gastrointestinal tract.

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Dose Schedule and Antitumor Studies of Arabinosyl Cytosine (NSC 63878)


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