A Clinical Evaluation of Dose and Schedule of Administration of Cytosine Arabinoside (NSC 63878)

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SUMMARY

Cytosine arabinoside (1-β-D-arabinofuranosylcytosine hydrochloride) was given to 24 patients with varied tumors for 32 trials in a study designed to compare toxicity of continuous infusion and single daily injections for a 5-day period. At low dose ranges of 50 and 100 mg/sq m, continuous infusion produced greater bone marrow depression than single injections. However, as dosage was increased from 150 to 300 mg/sq m, equal depression was encountered with either schedule. Increasing the dose to 400 and 600 mg/sq m by injection produced no further myelosuppression. Except for mild nausea and occasional vomiting, no other toxicity was encountered. The importance of varying treatment schedules in cancer chemotherapy is discussed.

INTRODUCTION

Cytosine arabinoside (ara-C; 1-β-D-arabinofuranosylcytosine hydrochloride), NSC 63878, is a unique synthetic pyrimidine nucleoside which contains arabinose substituted for ribose as the abnormal moiety. It is active against animal tumors, and human acute leukemia and lymphoma (7, 9, 10, 14). An optimal clinical dose schedule has not been established. This study was designed to compare continuous intravenous infusions and acute intermittent injections at several dosage levels for both toxicity and antitumor effect.

MATERIALS AND METHODS

Twenty-four patients with 15 varied tumor types received 32 trials with ara-C (Table 1).

All patients with advanced malignant disease were alternately allocated to either a continuous infusion of ara-C in 100 ml of 5% dextrose in water, or acute intravenous injections of drug diluted to 20 mg/ml at 24-hr intervals for 5 days. The daily dosage was fixed for each trial and ranged from 50 mg/sq m per trial through the maximum dose of 600 mg/sq m (Table 2). Patients were assigned to progressively higher dose levels based on experience accumulated. All evaluated patients were hospitalized and followed until evidence of drug effect had disappeared.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>10</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
</tr>
<tr>
<td>Prostate</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>1</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1</td>
</tr>
<tr>
<td>Renal cell</td>
<td>1</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Stomach</td>
<td>3</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Synovial cell</td>
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<tr>
<td>Hodgkin's</td>
<td>2</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Reticulum cell</td>
<td>1</td>
</tr>
</tbody>
</table>

Number of trials of ara-C in various tumors.

<table>
<thead>
<tr>
<th>Dosage levels (mg/sq m)</th>
<th>Infusion</th>
<th>Injection</th>
</tr>
</thead>
</table>
| 50                      | 3
| 100                     | 5         | 5         |
| 150                     | 1         | 4         |
| 200                     | 0         | 4         |
| 250                     | 1         | 1         |
| 300                     | 3         | 2         |
| 350                     | 0         | 2         |
| 400                     | 0         | 1         |
| 600                     | 0         | 1         |

Dosage levels, schedules and number of trials of ara-C in 24 patients with various tumors.

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RESULTS

White Blood Cells. In each patient, regardless of initial white blood count, dosage level or schedule, the white blood count followed a similar biphasic course. Two distinct nadirs were seen. Initial WBC fall occurred within 24 hr and continued through Days 7-9. A brief recovery period was again followed by a sharp WBC fall to the nadir occurring between Days 15-24. Nadir I occurred at a WBC of 5,200 on Day 7.3 (mean), with subsequent zenith I at 6,450 on Day 12.4. Nadir II was 2,500 on Day 20.3, with rapid ascent to zenith II. In each case following the second nadir, recovery to levels of 4,500 total cells was reached within 3 days with subsequent overshoot, then stabilization at pretreatment levels. Persistent leukemoid reactions were observed in three patients (Chart 1).

Readily apparent at low dose levels was the greater degree of bone marrow depression produced by the continuous infusion schedule. The relative WBC depressant effect of the two schedules at a dose of 100 mg/sq m is depicted in Chart 2.

Infusion at the 100 mg/sq m dose level produced significantly greater depression of both nadirs of the WBC curve, as well as greater rebound recovery. However, as dosage increased to 200 mg/sq m and above, similar degrees of depression were seen (Chart 3).

Similar WBC depression followed the minimum infusion dosage of 50 mg/sq m, and the maximum infusion dose of 300 mg/sq m. However, when equivalent doses were given by injection there was a relationship between the drug dose and the time of occurrence and the degree of WBC depression, as well as the magnitude of zenith. Beyond dosage of 250 mg/sq m, however, no difference attributable to drug amount could be established.

No greater marrow depression was observed in two patients given doses of 400 and 600 mg/sq m by injection (Chart 4).

Platelets. At all dose levels in both schedules the time of the nadir was similar, occurring between Days 12-13, mean 12.6, with recovery to greater than 100,000 platelets within 48 hours in all cases. Although at doses greater than 100 mg/sq m further depression of the platelet count could not be related to the dose given, the zenith at rebound was greater with peak counts of more than 2 million/μl at maximum doses (Chart 5).

The platelet count nadir coincided with the initial WBC zenith on Day 12.4, and the platelet zenith occurred at the time of the greatest WBC depression at all dose levels and schedules. The grand mean WBC and platelet counts are plotted in Chart 6.

Red Blood Cells. The percent of reticulocytes decreased rapidly and completely disappeared by Day 5. Recovery and subsequent rebound occurred between Days 18-21. The mean hemoglobin fall was 3 gm/100 ml during the period of study.

Bone Marrow. Random bone marrow aspirations revealed

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Chart 1. The grand mean of the WBC means produced by ara-C dosages of 50-600 mg/sq m given by infusion and injection. A characteristic configuration with minor and major nadirs and zeniths is seen. X represents the mean value of the means of the WBC at the various dose levels.
Chart 2. Comparative effect on peripheral white count of continuous 5-day infusion versus acute daily injection at 100 mg/sq m dosage level of ara-C. X and O are the mean WBC values of the patients treated at that level.

Chart 3. Comparative effect on peripheral white count of continuous infusion versus injection at 300 mg/sq m dosage level of ara-C. X and O represent the mean WBC values of the patients at that dose level.
Clinical Evaluation of Cytosine Arabinoside

the previously described megaloblastic alterations of the white and red cell precursors (1, 16), as well as similar changes in the megakaryocytes. These alterations were present in specimens obtained within 24 hours of inauguration of therapy, and continued through the course of treatment.

Other Toxicity. Both schedules and all dose levels were tolerated reasonably well. Gastrointestinal toxicity was manifested by nausea and occasional vomiting occurring after the rapid injection, and lasting not longer than 3 hours in any case. Prolonged anorexia was evident with the continuous infusion. Neither pain at the site of injection, stomatitis, nor diarrhea were encountered.

Hepatic dysfunction, monitored by weekly laboratory determinations of SGOT, SGPT, LDH, prothrombin time, bilirubin and total protein, was not encountered in this limited series.

Neither clinical nor laboratory evidence of renal impairment was discovered.

Antitumor Response. Twenty-four patients with measurable tumor were evaluated. No decrease in tumor size was seen.

DISCUSSION

ara-C inhibits the growth of various animal tumors, including intracerebrally implanted L1210, and is active against DNA viruses (12, 15, 17). Studies in man have revealed antitumor effect in human neoplasms. Evidence of significant antileukemic effect in both children and adults is being accumulated (4, 11). These studies have shown that ara-C is myelosuppressive, and that it will induce megaloblastosis and chromosomal disruption (1, 2, 4, 16).

Fischer and Chu have demonstrated the mechanism of anti-DNA activity to be a competition with deoxycytidine for deoxycytidine kinase (5), an effect reversed by deoxyeytidine ribotide (8). This mechanism of action infers that cell death results when cells being exposed to ara-C are passing through the S phase of their cell cycle. There is also evidence of blockage of the reduction of cytosine diphosphate to deoxyeytosine diphosphate, as well as a possible direct effect resulting in acute cell death (5, 6). Cytogenetic observations (2) have disclosed that ara-C will induce chromosomal breaks in G2, a portion of the cell cycle in which no DNA synthesis occurs. This effect is not causally related to the inhibition of DNA synthesis. Because the chromosome aberrations cause a delay in the procession of S cells to metaphase, the cells become mitotically synchronized. Antitumor effects in animals suggest that frequent small doses are superior to single daily injections (13, 18). Studies by Kline et al. (personal communication) in the mouse leukemia L1210 model indicate that, with ara-C, a therapeutic advantage may be provided with an intermittent schedule employing repeated courses of daily treatment with high doses interspersed with periods of no treatment, as compared with continuous daily treatment with low doses. This

Chart 4. Comparative effect of doses of ara-C of 50-600 mg/sq m given by injection and infusion on the major WBC nadir. Each point represents the WBC nadir observed during a single trial.
suggests that the superior response with intermittent therapy results from the ability of the host to tolerate more total drug, thereby increasing the degree of damage to the leukemic cell population.

In man, ara-C is rapidly deaminated by liver and kidney, and excreted as uracil arabinoside, an apparently inert compound. Detectable blood levels of ara-C are measurable only in the first hour following a single injection (7).

The results of this clinical study confirm that at doses of 50 and 100 mg/sq m given for five days, the prolonged maintenance of ara-C blood levels by constant infusion produced greater bone marrow depression than when given by the single injection schedule. Considering the drug deamination and excretion data available, this is a reasonable finding. However, at dosage ranges of 200 mg/sq m and greater, there was no significant difference between dose level and schedule as monitored by peripheral blood counts. Further increase in drug by injection through dosage ranges of 400 and 600 mg/sq m produced no intensification of suppression. There was no difference discovered at any of the constant infusion dosage ranges from 50 through 350 mg/sq m. Although the number of trials at various dose levels was small, it seemed that a drug concentration was reached above which greater bone marrow suppression by either infusion or single injection was not encountered. It is conceivable that during the brief exposure to active ara-C all available cells replicating DNA were affected, while cells in G1 and G2 were less affected.

Skipper and coworkers (personal communication) have shown in the L1210 tumor system (generation time, 12 hr and S phase, 8 hr) that ara-C given in short intensive intermittent schedules (24 hr every 4 days) produces a maximal therapeutic response and may result in tumor cures. Recent observations...
employing micropenic spleen colony-forming units indicate that more frequent administration of this drug produces greater selectivity in reduction of L1210 leukemia cells over that of normal bone marrow cells (I. Wodinsky, personal communication). These results support the hypothesis of Bruce et al. (3) that compounds which act at a particular phase of the cell cycle display a greater differential cytotoxic effect on normal hematopoietic and lymphoma cells when administered more frequently.

The present study demonstrates that, in man, maximal marrow toxicity is produced by doses of ara-C of 150 mg/sq m when administered for 5 days by either infusion or injection. Further dose increase does not intensify this toxicity.

Dose and schedule manipulations such as these are of practical importance if improvement in the therapeutic index is to be achieved. It may be possible to exploit kinetic or cell cycle differences which might exist between neoplastic and normal host cells. Selective antitumor effect without irreversible marrow suppression would be expected in rapidly growing tumors, such as Burkitts, choriocarcinoma and some leukemias, if most tumor cells were continually synthesizing DNA, whereas some normal marrow cells were resting in G1 or G2.

In the present study, erythropoiesis was effectively arrested at levels devoid of other obvious toxicity, suggesting the possible value of this compound in the treatment of polycythemia rubra vera. Although no specific tumor regression was observed in this study, the series was too small and tumor types too varied to permit a significant statement regarding the antitumor efficacy of this compound.

REFERENCES


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