Cancer Chemother Pharmacol (1982) 8:285–291

Cancer Chemotherapy and Pharmacology

Intrathecal Cytosine Arabinoside for the Treatment of Meningeal Metastases from Malignant Brain Tumors and Systemic Tumors

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Summary. *Thirty-two patients with primary or metastatic neoplasms in the ventricular system or subarachnoid space were treated with intrathecal Ara-C. Twenty patients (group I) were treated with single twice-weekly doses; the mean number of doses was 9.7, and the mean total dosage was 165 mg. Six patients received intrathecal Ara-C alone and 14 received concurrent chemotherapy. All four symptomatic patients showed clinical improvement. Malignant cells disappeared from the spinal fluid of six of the 12 patients with positive pretherapy cerebrospinal fluid (CSF) cytology. Two patients were alive with no evidence of recurrence 8 and 16 weeks after beginning therapy, two patients died without demonstrating evidence of recurrence 8 weeks and 9 weeks after starting therapy, 12 patients had recurrences an average of 13 weeks after beginning treatment, and four patients refused further investigation or treatment and died of disease after 6–52 weeks.*

Pharmacokinetic studies were performed in eight patients. For five patients who received 12 mg Ara-C by injection into an SC-implanted reservior connected to the ventricular system, the CSF disappearance curve was biphasic with half-times of 30 min and 3.5 h.

Based on the results of the pharmacokinetic study, an additional 12 patients (group II) were treated on three consecutive days weekly. The mean number of doses was 9.7 and the mean total dosage was 189 mg. Three patients received intrathecal Ara-C alone and nine received concurrent chemotherapy. One of the five symptomatic patients showed clinical improvement. Malignant cells disappeared from the spinal fluid of two of the four patients with positive pretherapy CSF cytology. Four patients were alive with no evidence of recurrence 3–26 weeks after beginning therapy, two patients died within 10 days of beginning treatment without formal re-evaluation, four patients demonstrated progression of tumor an average of 7 weeks after beginning treatment, and two patients changed to another form of therapy because of persistent CSF abnormalities, although there was no radiographic evidence of tumor progression.

There were no clear differences in response between group I and group II; however, the groups were not comparable with respect to pathological diagnosis.

Intrathecal Ara-C is a promising and relatively safe treatment for malignant disease in the subarachnoid space. Further studies are needed to determine the optimum dose and administration schedule in combination with other intrathecal therapies that may be more active against noncycling G_0 cells.

Introduction

Ironically, as aggressive treatment with radiation therapy and chemotherapy prolongs survival for patients with extracranial malignant tumors, meningeal involvement from metastases is being found more frequently [4, 13, 15]. Prolonged survival may also explain the apparent increase in the frequency of cerebrospinal fluid (CSF) seeding from primary central nervous system (CNS) malignancies.

CSF pathways offer a unique route for the administration of chemotherapeutic agents against malignant meningeal disease. Methotrexate (MTX) and cytosine arabinoside (Ara-C) are the most frequently used of the few drugs tested intrathecally

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0344-5704/82/0008/0285/$ 01.40

[1, 3, 9, 14]. However, while MTX has been tested extensively in a clinical setting against a broad spectrum of meningeal malignancies, including spread from primary CNS tumors, despite advantageous pharmacologic properties Ara-C has not been so extensively tested.

The half-time of Ara-C in CSF is longer than the half-time in plasma, because of the low activity of Ara-C deaminase in CSF. When given by continuous IV infusion, the steady-state Ara-C CSF-to-plasma ratio is 0.4 [8]. Because intrathecal injection of Ara-C results in extremely low plasma levels, intrathecal Ara-C treatment can be given intermittently and at lower doses than would be required with IV therapy. There is little risk of systemic toxicity and no need for IV infusion, which makes out-patient treatment feasible. Because of transcapillary elimination, Ara-C will not accumulate in CSF, even in patients with CSF outflow obstruction; Ara-C should be less toxic to the CNS than MTX.

We report here the effectiveness of intrathecal Ara-C treatment of patients with primary meningeal metastases from brain tumors and several systemic tumors, and the human pharmacokinetics of Ara-C after intrathecal administration.

Materials and Methods

Clinical Studies. To be eligible for this study, patients had to meet one or more of the following criteria: positive CSF cytology, positive myelographic evidence of drop metastasis, and/or computed tomography (CT) evidence of subarachnoid or ventricular spread. Thirty-two patients from our Neuro-oncology Service were treated with intrathecal Ara-C. In the initial part of the study, 20 patients (group I) with the following tumor types were treated: 11 with medulloblastoma, six with malignant glioma, and one each with primary intracranial germinoma, malignant melanoma, and lymphoma. Following completion of the initial portion of the clinical study and the pharmacokinetic evaluation, an additional 12 patients with the following tumor types were treated with Ara-C according to a different schedule (group II): five cases of glioblastoma multiforme, two of medulloblastoma, two of malignant glioma, two of metastatic carcinoma from an unknown primary lesion, and one of ependymoma. All tumors were located in the subarachnoid space, as indicated by the presence of malignant cells in the CSF or by radiographic evidence of the presence of tumor adjacent to the ventricular system or in the spinal subarachnoid space. Most patients were asymptomatic; however, in group I three had radicular pain and one had cranial nerve deficits, while in group II five had back and radicular pain that could be attributed to the presence of tumor in the subarachnoid space. Patients were evaluated by clinical neurological examination, radionuclide and CT brain scans, myelography when indicated, and by examination of the CSF for malignant cells and protein and polyamine levels.

In group I, six patients were treated with intrathecal Ara-C alone and 14 received concurrent systemic chemotherapy. Two patients received Ara-C by lumbar puncture alone and the remainder by puncture of a SC reservoir connected to the ventricular system. In group II, three patients were treated with intrathecal Ara-C alone, and nine received concurrent chemotherapy. Ten of these patients were treated via a ventricular reservoir and two were treated via a reservoir connected to the lumbar subarachnoid space. In patients who had a ventriculoperitoneal shunt, the on-off valve connecting the reservoir to the shunt tubing was closed before the Ara-C injection and opened approximately 6 h later, or earlier if the patient showed symptoms of increased intracranial pressure.

For group I patients, the dose was 12 mg twice weekly for 4 weeks, once weekly until the CSF cytology became negative, then once monthly. Our decision to treat at 12 mg was based on unpublished pharmacokinetic data from the Upjohn Company. Because of a lack of toxicity, each dose was increased to 20 mg during the study. Patients received an average of 9.7 doses (range 2–16) for an average total dosage of 165 mg (range 40–320 mg). For group II patients, the dose was 20 mg daily on three consecutive days, repeated weekly. Patients received an average of 9.7 doses (range 3–18) to give an average total dose of 189 mg (range 60–360 mg).

Pharmacokinetic Studies. Pharmacokinetic studies were conducted in eight patients in whom Ara-C was administered via a ventricular reservoir. CSF was obtained by puncture of the reservoir at various times after Ara-C injection. Ara-C levels in CSF were measured by means of a specific microbiological assay that has no cross reactivity for uridine arabinoside and has a sensitivity limit of 0.06 μg/ml. The disappearance of Ara-C from CSF was fit to a biexponential equation by means of a nonlinear iterative computer program (NONLIN).

Results

Clinical Studies

Response to Therapy. All four symptomatic patients in group I showed clinical improvement. One of the five symptomatic patients in group II experienced dramatic improvement in back and radicular pain caused by subarachnoid spread of a malignant glioma (Table 1).

As many patients as possible in both groups were followed until recurrence or death. Of the six patients in group I treated with intrathecal Ara-C alone, two developed intraparenchymal disease 4 weeks and 24 weeks after beginning intrathecal therapy, one developed a recurrence in the spinal subarachnoid space 8 weeks after starting therapy, one developed increased tumor enhancement in the wall of the lateral ventricle 3 weeks after initiation of therapy, and two refused further evaluation or therapy. Of the 14 patients who received concurrent systemic chemotherapy, one is free of recurrence 82 weeks after initiation of therapy, one changed to intrathecal MTX therapy after 8 weeks because of the persistence of malignant cells in the CSF, one died of aspiration pneumonia, one died from meningitis without evidence of tumor recurrence, eight demonstrated recurrence of tumor, and two refused further eval-

Table 1. Results of treatment with intrathecal Ara-C: Clinical improvement and recurrence

Treatment	Clinically improved	Alive, no recurrence	Dead, no recurrence	Recurred[a]	Refused further evaluation[b]
Group I					
Intrathecal Ara-C only	1/1	0/6	0/6	4/6	2/6
Intrathecal Ara-C plus[c]	3/3	2/14	2/14	8/14	2/14
Total	4/4	2/20	2/20	12/20	4/20
Group II					
Intrathecal Ara-C only	0/2	1/3	0/3	2/3	0/3
Intrathecal Ara-C plus[c]	1/3	5/9[d]	2/9	2/9	0/9
Total	1/5	6/12	2/12	4/12	0/12

[a] All recurrencences in patients who had not refused further evaluation occurred while receiving intrathecal Ara-C

[b] Died of tumor 6–52 weeks after refusing to continue on the study

[c] Plus systemic chemotherapy

[d] Two of these patients had no demonstrable tumor progression, but therapy was changed because of CSF polyamine elevation (both patients) and persistently positive CSF cytology (one patient) (see text)

uation or therapy. Of the patients who had recurrences, three demonstrated parenchymal recurrence, four demonstrated tumor recurrence in the subarachnoid space, and one demonstrated both parenchymal and subarachnoid space recurrences. Four of the five patients with recurrent tumor in the subarachnoid space were still receiving intrathecal Ara-C at the time of recurrence. The mean time to recurrence was 13 weeks (range 6–28 weeks) (Table 1). All four patients who refused further evaluation or treatment for social reasons died 6–52 weeks after refusing to continue.

In group II, recurrence has occurred in two of the three patients treated with Ara-C alone, and one patient with glioblastoma multiforme and positive CSF cytology shows no sign of progression after 8 weeks of intrathecal Ara-C treatment. Of the patients treated with concurrent chemotherapy, two had recurrences in the spinal canal after 2 and 3 weeks of treatment, two patients with glioblastoma multiforme adjacent to the ventricular system show no signs of tumor progression 3 and 8 weeks after commencing therapy, one patient stopped intrathecal Ara-C treatment after 26 weeks because of side-effects, two patients died within 10 days of beginning therapy (one of pulmonary embolism, one from hemorrhage into the tumor, a medulloblastoma) before repeat evaluation, and two patients who did not show clear progression of tumor were changed to another intrathecal medication because of persistently elevated CSF polyamine levels after 6–8 weeks of therapy. There was no difference in mean time to recurrence between patients harboring medulloblastoma and those harboring malignant glioma.

The only complication was the development of meningitis/ventriculitis in one patient, which resolved following antibiotic therapy and removal of the reservoir. Only one patient experienced side-effects. This 32-year-old male with subarachnoid spread of malignant glioma experienced headache, fever, and meningismus that lasted several days after each intrathecal injection.

CSF Cytology and Protein Levels. In group I, twelve patients had malignant cells in the CSF before initiation of treatment, two of whom developed positive cytology while receiving systemic chemotherapy. Three patients were not receiving any form of chemotherapy at the time of appearance of malignant cells in the CSF; treatment with systemic chemotherapy for periods ranging from 10 to 32 weeks did not clear the CSF of malignant cells. In six of the 12 patients with malignant cells in the CSF before initiation of treatment, CSF cytology became negative an average of 5 weeks (range 3–7 weeks) after the onset of therapy. One patient harboring a germinoma whose CSF cytology became negative was treated with intrathecal Ara-C alone. The other five patients whose CSF cytology became negative (three patients harbored medulloblastoma and two patients harbored malignant glioma) were treated with concurrent chemotherapy. One patient harboring a malignant glioma had negative CSF cytology when therapy began, but it became positive after 29 weeks while the patient continued to receive intrathecal Ara-C (Table 2).

In group II, four patients had malignant cells in the CSF before initiation of treatment. In two

patients (one with glioblastoma multiforme, one with malignant astrocytoma), the cytology became negative after three doses of Ara-C. In the other two patients (both carcinomatous meningitis), the CSF remained positive for malignant cells. One of these patients died of pulmonary embolism after two courses of therapy and one patient was changed to another intrathecal chemotherapeutic agent when he failed to respond to nine doses of Ara-C given in 3 weeks.

CSF protein levels fell during treatment in seven patients and rose at or before the time of recurrence in six patients (Table 3).

CSF Polyamines. CSF putrescine (Pu) and spermidine (Sp) levels both fell during treatment in nine patients, three of whom had malignant glioma, four medulloblastoma, and one each malignant melanoma and glioblastoma multiforme (Table 4). This group included two patients whose CSF cytology was positive for malignant cells before treatment and became negative during treatment. In one patient with medulloblastoma whose CSF cytology became negative during treatment, CSF Pu − but not Sp − fell during treatment. In the rest of the patients in whom malignant cells disappeared from the CSF during treatment, CSF polyamines were not evaluated during treatment. In four of five patients in whom clinical improvement occurred during therapy, CSF polyamines were not evaluated. In the fifth patient polyamine levels remained stable but elevated during therapy.

Both Pu and Sp levels rose at the time of tumor progression in 12 of 14 patients with evaluable CSF polyamine levels, five harboring medulloblastoma, four malignant glioma, two glioblastoma multiforme, one meningeal carcinomatosis, one ependymoma, and one metastatic malignant melanoma.

Polyamine levels in one patient were of particular note. This 18-year-old male was treated with intrathecal Ara-C via a ventricular reservoir because of a cauda equina metastasis of medulloblastoma. During treatment, polyamine levels in the lumbar CSF decreased and his root pain disappeared. Lumbar CSF polyamine levels increased before evidence of recurrence. In contrast, polyamine levels in the ventricular fluid rose steadily during treatment and eventually a recurrent tumor in the posterior fossa was demonstrated.

Table 2. Results of treatment with intrathecal Ara-C: CSF cytology

Treatment	Malignant cells present before therapy	Cytology became negative during therapy
Group I		
Intrathecal Ara-C only	2	1
Intrathecal Ara-C plus[a]	10	5
Total	12	6
Group II		
Intrathecal Ara-C only	1	1
Intrathecal Ara-C plus[a]	3	1
Total	4	2

[a] Plus systemic chemotherapy

Pharmacokinetic Studies

Data for all eight patients studied are summarized in Table 5. The CSF disappearance curve for the six

Table 3. Results of treatment with intrathecal Ara-C: CSF protein

	N	During treatment				At recurrence[a]			
		Decreased	Stable	Increased	Not evaluable[b]	Lower than pre-treatment	Unchanged	Higher	Not evaluable[b]
Group I									
Ara-C only	6	2	0	0	4	0	1	1	4
Ara-C plus[c]	14	2	7	1	4	2	4	3	3
Group II									
Ara-C only	3	1	0	1	1	0	0	1	1
Ara-C plus[c]	9	2	1	1	5	0	0	1	3

[a] Two patients in group I and six patients in group II did not experience any recurrence
[b] The seven patients in group I died of tumor 6–52 weeks after refusing to continue on the study; two patients in group II died within 10 days of starting treatment before CSF re-evaluation
[c] Plus systemic chemotherapy

Table 4. Results of treatment with intrathecal Ara-C: CSF polyamines

Time of determination	*N*	Pu				Sp			
		De-creased[a]	Stable	In-creased[a]	Not evaluable[b]	De-creased[a]	Stable	In-creased[a]	Not evaluable[b]
Group I									
Intrathecal Ara-C only									
During treatment	6	2	0	[c]	3	2	1	0	3
At recurrence[d]	6	0	1	1	4	0	1	1	4
Intrathecal Ara-C plus[e]									
During treatment	14	6	1	1	6	5	2	1	6
At recurrence[d]	14	0	0	8	4	0	0	8	4
Group II									
Intrathecal Ara-C only									
During treatment	3	1	1	1	0	2	0	1	0
At recurrence[d]	3	0	0	2	0	0	0	2	0
Intrathecal Ara-C plus[e]									
During treatment	9	3	2	1	3	3	2	1	3
At recurrence[d]	9	1	0	1	2	0	2	0	2

[a] Compared with pretreatment values
[b] The seven patients in group I died of tumor 6–52 weeks after refusing to continue on study; the two patients in group II died within 10 days of starting treatment, before CSF re-evaluation
[c] See text
[d] Two patients in group I and six patients in group II did not experience any recurrence
[e] Plus systemic chemotherapy

Table 5. Intraventricular Ara-C pharmacokinetics

Patient	Dose (mg)	$\alpha t_{1/2}$ (min)	$\beta t_{1/2}$ (min)	V_{DB}[a] (ml)	AUC[b] (mg · min/ml)
1	12	12.4	53.4	33	56.0
2	12	17.5	172.3	206	49.9
3[c]	12	–	–	–	43.6
4	12	22.0	103.8	32	79.6
5	12	9.0	85.2	63	30.1
6	12	11.9	88.8	117	15.5
7	20	13.4	99.3	93	36.6
8	24	15.2	93.6	82	56.2
Mean		14.5	99.5	90	46.0 (189 m*M* · min)
SE		1.6	13.6	23	6.9 (28 m*M* · min)

[a] V_{DB} = dose/B, where dose = μg/ml and B = μg/ml
[b] AUC = $A/\alpha + B/\beta$, where CSF levels of Ara-C (C_{CSF}) were computed by nonlinear iteration and $C_{CSF} = Ae^{-\alpha t} + Be^{-\beta t}$
[c] This patient had a ventricular-peritoneal shunt with an on-off valve that was occluded before injection of Ara-C and opened 6 h later

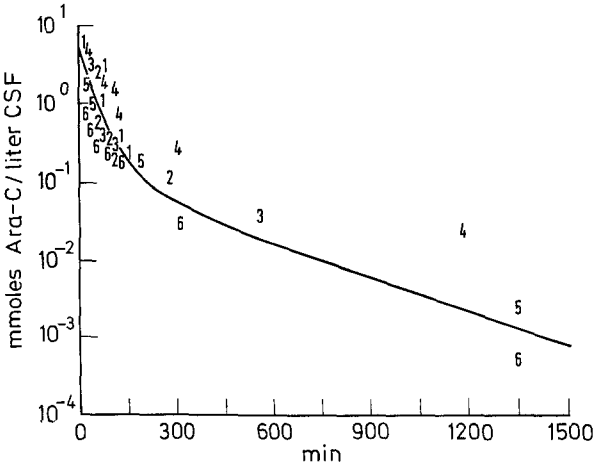

Fig. 1. CSF Ara-C levels in six patients following a dose of 12 mg. The drug was administered via a ventricular reservoir. Patient numbers are as in Table 5. The curve was fit to a biexponential equation by means of a nonlinear iterative computer program. The half lives from this curve were 30 min and 3.5 h; these values differ from those listed in Table 5, which were the average computed for each patient

patients who received 12 mg Ara-C via a ventricular reservoir was biphasic, with a mean initial fast phase half-life of 30 min and a slower second phase half-life of 3.5 h (Fig. 1). The volume of distribution for Ara-C in CSF (V_{DB} area) varied between 16 and 99 ml, which indicated a sizeable variation in the volume of CSF accessible to Ara-C; the normal adult CSF volume is approximately 140 ml. Clearance was first order without CSF accumulation for multiple doses administered on successive days.

Discussion

Clinical Studies

Treatment with intrathecal Ara-C is safe and can improve clinical symptoms caused by malignant disease in the subarachnoid space. In two patients, improvement followed treatment with Ara-C alone, which ruled out a therapeutic effect from systemic chemotherapy administered concomitantly with Ara-C to most patients in both groups.

Treatment with intrathecal Ara-C did not prevent the development of metastatic disease in the subarachnoid space. In the absence of a control group, we could not determine whether metastases were reduced or delayed by intrathecal Ara-C treatment. However, intrathecal Ara-C chemotherapy alone can cause malignant cells to disappear from the CSF.

All patients whose CSF polyamine levels were evaluable at the time of recurrence had elevated levels of Pu or Sp. Both were elevated in 12 of 14 patients with evaluable polyamine levels. Although the patient group is small, the data agree with the excellent correlation between elevated CSF polyamine levels and clinical recurrence found in patients with medulloblastoma [12] and with a good correlation between CSF polyamine levels and clinical status in patients with meningeal carcinomatosis [17]. Elevated CSF polyamine levels also have been found in patients with malignant glioma adjacent to the ventricular system and subarachnoid space, and may correlate with tumor recurrence [5]. In addition, in one patient a correlation was found between the origin of elevated CSF polyamines (lumbar or ventricular CSF) and the site of recurrence.

Only one serious complication (an infection) was found in 311 treatments, which indicates the safety of this therapeutic approach. Only one patient experienced side-effects severe enough to discontinue therapy after three courses of therapy (nine treatments).

Because of the small numbers of patients and the fact that the two groups were not exactly comparable with respect to diagnosis, we could not demonstrate any difference in response of the group of patients treated on three consecutive days (group II) instead of twice weekly (group I). Data listed in Table 1 suggest that, because there were fewer recurrences (12/16 vs 4/12), group II patients might do better.

We believe that analysis of the CSF for cytology and polyamines is an accurate method for evaluating response to intrathecal chemotherapy, even when patients are receiving concomitant systemic chemotherapy. In this series, two patients developed positive CSF cytology while undergoing systemic chemotherapy, and three patients with positive CSF cytology did not respond to systemic chemotherapy alone. Of all the patients with positive CSF cytology seen on our Service, *in none have malignant cells disappeared from the CSF following treatment with systemic chemotherapy alone.* This lack of response to systemic chemotherapy probably results from inadequate CSF drug penetration and/or low CSF drug exposure integrals (C×T) following systemic administration [11]. Thus it is probable that the drug exposure dose in the subarachnoid space is insufficient to kill malignant cells and produce a clinical response.

In groups I and II, the intrathecal Ara-C/systemic chemotherapy subgroups did slightly better than the intrathecal Ara-C only subgroups. However, the subgroups are too small for statistical analysis.

Pharmacokinetic Study

The in vitro susceptibility of human brain tumors to Ara-C has not been determined. Mouse L1210 leukemia cells require a 12-h exposure to 2.8 μg Ara-C/ml (11.5 μmoles/l) or a 24-h exposure to 0.1 μg/ml (0.4 μmoles/l) to achieve greater than 49% cell kill [16]. Mouse L cells require a 24-h exposure to 10 μg Ara-C/ml (41 μmoles/l) to produce a 99% cell kill [6]. The CSF concentration of Ara-C in our patients fell below 41 μmoles/l at approximately 6 h, below 11 μmoles/l after 12 h, and below 0.4 μmoles/l at approximately 28 h (Fig. 1). Even though the initial CSF concentrations of Ara-C were very high, it is possible that the time of exposure was too short to achieve adequate levels to kill all cycling cells. In addition, because the number of cycling cells in meningeal infiltrates is probably low [10], Ara-C efficacy may be restricted severely even in the face of otherwise adequate CSF levels.

As a consequence of this study, we modified our schedule for intrathecal Ara-C administration to three consecutive daily treatments with 20 mg, which should provide CSF Ara-C levels above 1.5 μmoles/l

for over 72 h. Many therapists administer 100 mg intrathecally; a single dose would produce CSF Ara-C levels above 1.5 μmoles/l for only 32 h. A dose of 20 mg on three consecutive days achieves adequate therapeutic levels for longer periods with only 60% of the conventional intrathecal Ara-C dose.

The variation in the volume of distribution (V_D area) of Ara-C indicates that the entire CSF volume (approximately 140 cm^3) is not accessible to Ara-C. Because therapy failure may result if tumor cells adjacent to CSF pathways are not exposed to drug, we suggest that radionuclide-labeled albumin be injected into the reservoir and followed throughout the spinal and cranial subarachnoid space before initiation of therapy, to be certain that subsequent Ara-C treatments will be effective. In the occasional presence of a spinal block to CSF flow, a lumbar as well as a ventricular reservoir should be surgically implanted.

Conclusions

Ara-C is a promising drug for the intrathecal chemotherapy of patients with meningeal or ventricular spread of primary and metastatic brain tumors. Treatment can cause resolution of symptoms and clear the CSF of malignant cells. Further studies with larger numbers of patients are needed to compare the response rate following intrathecal Ara-C treatment alone to intrathecal Ara-C drug combinations with other drugs such as MTX and thio-TEPA. In addition, combined pharmacokinetic and in vitro cytotoxicity studies must be performed to further define the optimum schedule for intrathecal Ara-C administration.

Acknowledgements. Supported in part by National Cancer Institute Program Project Grant CA-13525 and American Cancer Society Faculty Research Award FRA-155 (Victor A. Levin).

We are deeply indebted to the neurosurgeons in private practice and at the Kaiser-Permanente Medical Centers of the Greater Bay Area for referring patients to us. We thank Dr Laurence J. Marton and Mr Warren Lubich for CSF polyamine measurements, Beverly H. McGehee for preparation of the manuscript, and Neil Buckley for editorial assistance.

References

1. Band PR, Holland JF, Bernard J, Weil M, Walker M, Rall D (1973) Treatment of central nervous system leukemia with intrathecal cytosine arabinoside. Cancer 32: 744
2. Blasberg RG, Patlak C, Fenstermacher JD (1975) Intrathecal chemotherapy: Brain tissue profiles after ventriculo-cisternal perfusion. J Pharm Exp Ther 195: 73
3. Bleyer WA (1977) Current status of intrathecal chemotherapy for human meningeal neoplasms. Natl Cancer Inst Monogr 46: 171
4. Evans AE, Gilbert ES, Zandstra R (1971) The increasing incidence of central nervous system leukemia in children. Cancer 26: 404
5. Fulton DS, Levin VA, Lubich WP, Wilson CB, Marton LJ (1980) Cerebrospinal fluid polyamines in glioblastoma multiforme and anaplastic astrocytoma. Cancer Res 40: 3293
6. Graham FL, Whitmore GF (1970) The effect of 1-β-D-arabinofuranosyl cytosine on growth, viability and DNA synthesis of mouse L-cells. Cancer Res 30: 2627
7. Hanka LJ, Kuentzel SL, Neil GL (1970) Improved microbiological assay for cytosine arabinoside. Cancer Chemother Rep 54: 393
8. Ho DHW, Frei E (1971) Clinical pharmacology of 1-β-D-arabinofuranosyl cytosine. Clin Pharmacol Ther 12: 944
9. Hyman CV, Bogle JM, Bribaker CA, Williams K, Hammond D (1965) Central nervous system involvement by leukemia in children. II. Therapy with intrathecal methotrexate. Blood 25: 13
10. Kuo AH, Yataganas X, Galicich JH, Fried J, Clarkson BD (1975) Proliferative kinetics of central nervous system (CNS) leukemia. Cancer 36: 232
11. Levin VA, Patlak CS, Landahl HD (1980) Heuristic modeling of drug delivery to malignant brain tumors. J Pharmacokinet Biopharm 8: 257
12. Marton LJ, Edwards MS, Levin VA, Lubich WP, Wilson CB (1979) Predictive value of cerebrospinal fluid polyamines in medulloblastoma. Cancer Res 39: 993
13. Nugent JL, Bunn PA, Matthews MJ, Ihde DC, Cohen MH, Gazdar A, Minna JD (1979) CNS metastases in small cell bronchogenic carcinoma. Cancer 44: 1885
14. Wang JJ, Pratt CB (1970) Intrathecal arabinosyl cytosine in meningeal leukemia. Cancer 25: 531
15. West RJ, Graham-Pole J, Hardisty RM, Pike MC (1972) Factors in pathogenesis of central nervous leukemia. Br Med J 3: 311
16. Wilkoff LJ, Wilcox WS, Burdeshaw JA, Dixon GJ, Dulmadge EA (1967) Effect of antimetabolites on the kinetic behavior of proliferating cultures of L1210 leukemia cells. J Natl Cancer Inst 39: 965
17. Yap BS, Yap HY, Nishioka K, Bodey GP (1979) Cerebrospinal fluid (CSF) polyamines and carcinoembryonic antigen (CEA) in meningeal carcinomatosis. (Abstract) Proc Am Assoc Cancer Res 20: 187

Received November 16, 1981/Accepted February 4, 1982