Cancer Chemother Pharmacol (1989) 23: 301–307

Cancer Chemotherapy and Pharmacology

Phase I/II study of intraventricular and intrathecal ACNU for leptomeningeal neoplasia*

Victor A. Levin, Marc Chamberlain, Pamela Silver, Luis Rodriguez**, and Michael Prados*****

Brain Tumor Research Center, Department of Neurological Surgery, University of California, San Francisco, CA 94143, USA

Summary. A total of 27 patients with leptomeningeal neoplasia were treated with the water-soluble nitrosourea ACNU given intraventricularly or intrathecally in a phase I/II study. Patients were entered in the study if they showed evidence of either a positive CSF cytology or neurodiagnostic evidence of leptomeningeal disease, or both. Patients were evaluated for toxicity and efficacy; additionally, in 13 patients ACNU pharmacokinetic studies were carried out. A variety of tumor types were represented in the study group, including primary and metastatic CNS tumors. Toxicity was mild and included pain at the injection site (four patients), transient radicular symptoms at a short distance from the injection site (three patients), and nausea and vomiting (one patient). No myelotoxicity was seen. Of 21 patients who presented with positive cytology, 8 (38%) had a conversion from positive to negative cytology, with a range of response durations from 1 to 20+ months. Of the remaining six patients with negative cytology but other neurodiagnostic evidence of leptomeningeal disease, one patient showed an improvement seen on the myelogram and one underwent a brief reduction in CSF protein. ACNU elimination from the ventricular system is rapid, with a beta slope of 0.028 min^{-1} and a computed elimination constant, K_o, of 13 min. The mean clearance was 3.8 ml/min (range, 1.0–6.2 ml/min). Peak ACNU levels varied between 108 and 620 μg/ml, with the AUC being 1.4–14.7 mg·min/ml. The total dose of ACNU given was between 9 and 104 mg, and the single dose range was 4–16.5 mg. We conclude that ACNU can be given safely with minimal toxicity as intra-CSF therapy, that it demonstrates efficacy in some patients with leptomeningeal disease, and that further studies are warranted to evaluate more fully alternative dosing and drug delivery approaches.

* Supported in part by HEW grant CA-13525

** American Cancer Society Regular Clinical Fellows at time of study

*** *Current address* of M. C. is Department of Neurosciences, University of California-San Diego Medical Center, San Diego, CA 92103, USA

Offprint requests to: Victor A. Levin, Department of Neuro-oncology, Box 118, University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA

Introduction

The treatment of leptomeningeal neoplasia is limited to irradiation of the brain and spinal cord and/or the use of a limited number of drugs that can be injected directly into the spinal subarachnoid space (intrathecally) or cerebral ventricles. Although irradiation of the brain is sometimes effective, as in CNS leukemia prophylaxis, it has toxic effects on the brain that result in intellectual impairment even at doses as low as 2500 rad [8].

Although helpful in many cases, intraventricular or intrathecal chemotherapy is generally palliative [3]. One reason for the limited success of drugs injected into the cerebrospinal fluid (intra-CSF) is the dearth of safe and efficacious drugs. In the United States, only three drugs – methotrexate [9, 14], cytosine arabinoside [1, 6, 15], and thio-TEPA [7] – are used.

In a recent study we evaluated the safety and efficacy of a number of chloroethylnitrosoureas (CENU) in a beagle model [12, 13] to determine whether a clinical phase I study of any of these drugs should be undertaken. From a theoretical point of view, the CENUs offer advantages over methotrexate and cytosine arabinoside in that the former are cell-cycle nonspecific in their mode of action and have a much broader spectrum of tumor activity than thio-TEPA. In that study we evaluated chlorozotocin, 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea (PCNU), and 1,3-bis-2-chlorethylnitrosourea (BCNU) to a limited extent and a water-soluble nitrosourea, ACNU [13], to a much greater extent. We found that of the four drugs, ACNU was tolerated best in the dogs and could be safely given at doses of 0.8 mg/week for 8 consecutive weeks. The CSF pharmacokinetics of ACNU in the dogs showed that the CSF elimination rate constant, K_o, was more rapid than the known rate of ACNU decomposition in CSF. This indicated that ACNU clearance from the CSF was effected by three factors: aqueous decomposition, transcapillary exchange, and cellular entry. We calculated that the drug exposure integral ($C \times T$) of ACNU in the CSF after a dose of 0.8 mg would be greater than 5 times that required to achieve in vitro cell kills well in excess of 3 logs for rat 9L and human glioma 126 cells. From those pharmacokinetic studies, we assumed that the only factor limiting antitumor efficacy would be that the rapid CSF elimination (half-life = 18 min) of ACNU is short compared with its equilibration time from the ventricle to the spinal- and cerebral convexity-subarachnoid

space. With this caveat in mind, we embarked on a clinical phase I trial of intra-CSF ACNU in patients with various meningeal neoplasms.

Materials and methods

Patients. Patients were evaluable for study if they showed documented evidence of a meningeal neoplasia such as CNS leukemia, medulloblastoma, glioma, or meningeal carcinomatosis. To be eligible for ACNU, patients had to meet the following additional criteria:

1. Life expectancy of >8 weeks
2. WBC $>3000/mm^3$ and platelets $>75{,}000/mm^3$
3. Liver and renal function tests <2 times normal values
4. Karnofsky Performance Status of $>60\%$
5. No concomitant radiation therapy to any part of the cranial-spinal axis
6. Understanding on the part of the patient (or responsible next-of-kin) as to the experimental nature of this therapy and submission of a signed informed consent form

Patients were staged according to the extent of their leptomeningeal disease using the following guidelines:

1. Stage 1 – cytology negative; clinical and/or neurodiagnostic evidence of cranial nerve, spinal root, spinal cord, or leptomeningeal disease
2. Stage 2 – cytology positive; no clinical or neurodiagnostic evidence of neuroaxis disease
3. Stage 3 – cytology positive and clinical or neurodiagnostic evidence of cranial nerve, spinal root, spinal cord, or leptomeningeal disease

Staging was determined by: (1) lumbar puncture for CSF cytology, cell count, protein, glucose, and markers determinations when indicated; (2) complete spinal myelography followed by spinal computerized axial tomographic (CAT) scans when indicated; (3) complete, contrast-enhanced CAT brain scans; and (4) spinal MRI scans.

In addition, prior to treatment by any intra-CSF route, a ^{99m}Tc-albumin CSF flow study was carried out to determine the patency of the CSF pathways, whether there is flow above the convexity (cerebral subarachnoid space), and the relative rates of flow from the injection site to the thoracic spinal subarachnoid space, cisterna magnum, and lateral ventricle. Some patients underwent quantitation of ^{99m}Tc-albumin flow using a computer to record the CPM/pixel over time and by region. These data were subsequently corrected for decay and used to compute regional (e.g., lateral ventricle, cisterna magnum, and thoracic cord) exponential clearance curves (Fig. 1).

Drug formulation and dose preparation. ACNU was supplied by Sankyo Company, Ltd. (Japan). Vials containing 25 mg lyophilized ACNU·HCl and 90 mg NaCl were econstituted with 2.5 ml sterile, preservative-free, distilled water (pH 3.1).

ACNU was injected by one or more of the following routes: lumbar puncture, cervical 1–2 space puncture, or into a ventricular reservoir (e.g., Foltz or Ommaya type) with sterile precautions and consideration for the light-mediated degradation of ACNU. While the needle was in place, CSF was aspirated into the drug-containing syringe and the entire mixture was injected over 15–30 s. If a ventricular reservoir was used, it was barbotaged four times to deliver the drug into the CSF, clear the reservoir and its tubing of ACNU, and provide rapid mixing in the CSF.

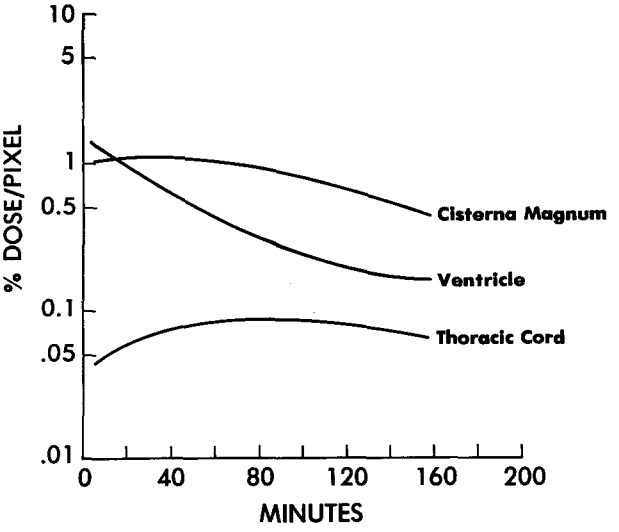

Fig. 1. Quantitative CSF distribution of ^{99m}Tc-albumin following intraventricular administration and barbotage. A collimator was placed over a lateral ventricle, the cisterna magnum, and thoracic cord; counts were accumulated and stored in a computer and were later corrected for decay and used to compute the percentage of the dose/pixel in the three regions over time

ACNU dose. Based on the toxicity studies conducted in beagle dogs [13] and the fact that the human/dog ratio of CSF volume is approximately 10 [3, 5], our initial study design was to treat at doses of 8 mg/week every other week for a total of four doses and, thereafter, monthly for up to four doses if tolerated and medically indicated. Studies in six patients indicated that this dose was tolerable, but that alternate-week therapy may be inadequate because of pharmacokinetics and rapid clinical deterioration and that weekly $\times 4$ weeks would be preferable. Subsequent patients were treated weekly $\times 4$ weeks at increasing doses, with higher doses being sought if neurotoxicity was not seen and the patient was stable or responding to the ACNU. Although we had originally hoped to use myelotoxicity as a toxicity endpoint, many patients required systemic chemotherapy for their CNS or systemic neoplasm; thus, this endpoint was neither reliable nor valid.

Measurement of effect. Tumor response or progression was measured directly by CSF examination or indirectly by various combinations of neurologic examination, CAT brain scan, and myelogram. Patients underwent reservoir and/or lumbar CSF examinations after two courses of ACNU and before the third dose at 2 weeks for cell count and cytology as well as protein, and glucose content. Patients were also evaluated by neurologic exam and CAT scans on their entry in the study and every 6–8 weeks thereafter until progression of disease or as medically indicated [11]. Spinal myelography or CAT scans were carried out for follow-up purposes as indicated. For all tests done, the determination of response or deterioration was based on changes that had occurred since the prior examination period.

Improvement in neurologic signs and symptoms coupled with objective improvement in myelography (or CAT spinal scan) or in CSF cytology and protein content were considered to represent an optimal response. Deterioration was defined as a worsening in the CSF cytology, an increase in CSF protein, worsening radicular or cranial

Table 1. Intra-CSF ACNU

Patient	Diagnosis	Concurrent treatment	Total dose (mg)	Doses/schedule	MG dose × treatment	
					(IV)	(IT or IC)
1	Medulloblastoma	8422-DBD	82	3/q.o. week, 1/q.o. week 3/q. week	4 × 3 5 × 1 8 × 3	4 × 3 5 × 1 8 × 3
2	MOAA (GM)[a]	8522-8422	12	3/q.o. week		4 × 3
3	Anaplastic astrocytoma	–	32	4/q.o. week	4 × 1 8 × 3	4 × 1
4	Melanoma	–	20	2/q.o. week	5 × 2	5 × 2
5	CUPS	CHOP, RT	17	2/q. month	5 × 1 5 × 1	5 × 1 2 × 1
6	Medulloblastoma	8422	90	6/q.o. week	5 × 1 8 × 5	5 × 1 8 × 5
7	Medulloblastoma	8422	12	2/q. week		4 × 1 8 × 1
8	Adenocarcinoma	–	60	2/q.o. week, 4/q. week		10 × 6
9	Medulloblastoma	8422A	40	4/q. week	10 × 4	
10	CML blast crises	HU	30	3/q. week		10 × 3
11	Lung adenocarcinoma	–	30	3/q. week	10 × 3	
12	Glioblastoma	8522	80	+4/q. week, 1/q.o. week 2/q.o. month	12 × 6	10 × 1
13	Glioblastoma	Melph	36	3/q. week	12 × 3	
14	Ovarian cancer	CDDP ADR	84	7/q. week	12 × 7	
15	Medulloblastoma	Melph	36	3/q. week	12 × 3	
16	Primary CNS lymphoma	HD Mtx	60	5/q. week	12 × 5	
17	Medulloblastoma	8422	43.5	3/q. week	13.5 × 1 15 × 2	
18	Malignant ependymoma	8422	72	4/q. week, 1/q.o. week	12 × 5	
19	Oligodendroglioma	RT-PCV	48	12/q. week, 8/q. week 8 × 1 day		12 × 2 8 × 3
20	ALL	PON, VCR	30	2/q. week	15 × 2	
21	Medulloblastoma	8422	64	16/q. week		16 × 4
22	Meningeal Carcinomatosis (MMG)	–	16.5	1/q. week	16.5 × 1	
23	Ependymoma	8422A	64	1/q. week	4 × 1 10 × 6	
24	Medulloblastoma	8422A	9		5 × 1	4 × 1
25	Lung Cancer Meningeal Carcinomatosis	–	75	1/q. week		15 × 5
26	Gastric Cancer	FU, Adria Mito-C	104	8/b.i. week × 5	8 × 13	
27	HAA	RT	6	6/q. week		6 × 1

[a] Transformed to GM

IV, intraventricular; IT, intrathecal; IC, cervical; 8422, 6TG/procarbazine/dibromodulcitol/CCNU/vincristine chemotherapy; 8522, 6TG/procarbazine/dibromodulcitol/CCNU/5FU/hydroxyurea chemotherapy; DBD, dibromodulcitol chemotherapy; RT, radiation therapy; Melph, p.o. melphalan; CHOP, cytoxan/adriamycin/procarbazine/vincristine chemotherapy; CDDP, cisplatin; ADR, adriamycin; HD Mtx, high-dose methotrexate

Schedule codes: q,. every; o., other

nerve signs and symptoms, or the occurrence of a new subarachnoid mass lesion. Time to progression was measured from the 1st day of treatment until progression was documented, at which time patients were removed from the study and treated with other appropriate therapy.

ACNU pharmacokinetics. Samples of CSF were taken at various times after either intraventricular (through Foltz or Ommaya reservoir) or intrathecal administration. CSF was removed from either the reservoir or a lumbar puncture, site depending on the route of administration.

Table 2. ACNU toxicity

Patient	Before treatment				After treatment				PNS[a]	Injection site pain	GI
	WBC	Hgl	Hct	Plt	WBC	Hgl	Hct	Plt			
1	4.6	13.5	39.6	218	4.3	11.9	34.2	148			
2	7.2	14.9	44.5	291	9.7	14.6	43.9	272			
3	–	–	–	–	–	–	–	–	X		
4	6.1	11.5	34.3	273	5.8	11.6	34	176		X	
5	5.3	10.7	30.8	nd	13.8	11.8	35.4	nd		X	
6	11.0	13.1	39.2	315	4.8	14.2	42.7	220	X	X	
7	2.4	13.5	38.8	363	2.0	11.2	32.1	234	X		
8	–	–	–	–	7.0	11.8	nd	160			
9	2.4	14	46	148	9.7	13.5	39.8	188			
10	22.4	15.8	46.9	850							
11	6.6	11.5	37.3	428		–	–	–			
12	15.5	14.5	41.9		8.2	14.1	40.7	274			
13	6.8	15.3	45	–	7.1	13.9	40.5	245			
14	4.0	12.8	–	adq	3.0	12.6	–	230			
15	5.9	10.6	34.2	274	6.6	11.7	37.4	225			
16	1.8	–	–	100	–	–	–	–			
17	3.8	12.1	36.4		3.8	11	35.7	328			
18	5.4	11.8	35.2	282	3.0	9.9	29.3	135			
19	–	–	–	–	5.6	13	41	233		X	
20											
21	4.8	12.9	37.0	201	4.6	12.6	37.2	235			
22	11.3		41.3	299							
23	1.8	9.6	28.0	adq	2.8	10.9	32.1	adq			
24	5.2	–	47	226							
25	8.6	13.5	40.8	209	4.4	10.5	30.6	–			X
26	8.4	12.1	36.8	590	5.5	13.3	39.0	319			
27	–	–	–	–	–	–	–	–			

[a] Transient painful radiculopathy with injection. Patient 4 also complained of mild fatigue; patient 25 had severe nausea and vomiting and was hospitalized for dehydration
Hgl, hemaglobin; Plt, platelets

The ACNU assay procedure was similar to that previously used [13]. The HPLC system consisted of a Perkin-Elmer Series 2 solvent delivery system, a Rheodyne model 7120 sample injection valve, a Brownlee HPLC precolumn guard system containing an RP-18, 5-μm, 3 cm × 4.6 mm (inside diameter) cartridge, an Alltech analytical HPLC column (RP-18, 5 μm, 25 × 4.6 mm inside diameter), a Beckman model 160 ultraviolet detector with a 254-nm fixed wavelength filter, and a Linear Instruments Corp. dual pen recorder.

HPLC grade methanol and acetronitrile, sodium acetate (anhydrous, reagent grade) and analytical grade glacial acetic acid were used. Distilled water was prepared in-house by redistillation in glass. The mobile phase for the reverse-phase column was 1:3 acetonitrile:water (acetate buffer, pH 4.4, 0.29 *M*) with a flow rate of 1.4 ml/min. CSF-ethanol samples of 0.03 ml were injected directly onto the HPLC. ACNU had a retention time of about 7.5 min. Standard curves of peak height vs. known concentration for five known samples was run with each batch of unknown CSF samples.

Under sterile conditions, CSF samples of 0.5 ml were removed from either a ventricular reservoir or a lumbar puncture site at timed intervals of 2, 4, 6, 10, 15, 30, 45, 60, and 90 min. The CSF samples were immediately placed into iced tubes containing 0.2 ml 95% ethanol. Samples were kept on ice in a dark environment until assayed the same day using the methods described above.

The descending plot of ACNU in μg/ml CSF (C_{csf}) against time was used to compute the area under the CSF curve (AUC) and the area under the moment curve (AUMC) with a computer program that applies a trapezoidal solution for the ascending portion of the CSF curve and a log-linear solution for the descending portion of the curve. The formulae used were those of Benet and Galeazzi [2] and Chan and Gibaldi [4].

$$V_{ss} = (\text{dose} \cdot \text{AUMC}/\text{AUC}^2) - \text{dose} \cdot T/2\text{AUC}, \quad (1)$$

$$CL_t = \text{dose}/\text{AUC}, \text{ and} \quad (2)$$

$$K_o = CL_t/V_{ss}, \quad (3)$$

where V_{ss} = the volume of distribution at steady state (ml), CL_t = the total CSF clearance (ml/min), K_o = the constant of drug elimination from CSF (l/min), and T = the duration of drug infusion (min). Since T is small (0.5–1.0 min),

$$V_{ss} = \text{dose} \cdot \text{AUMC}/\text{AUC}^2. \quad (4)$$

Results

Toxicity

Assessing the neurotoxicity and myelotoxicity of ACNU was not easy. Patients with meningeal neoplasia frequently have very complicated medical courses that require systemic cytotoxic chemotherapy, antibiotics, and psychosocially mediated treatment modifications. Table 1 summarizes the patients studied with respect to tumor histolo-

Table 3. Outcome of ACNU treatment

Patient	Diagnosis	CSF Prot	before Glu	treatment Cyt	CSF Prot	after Glu	treatment Cyt	Outcome
1	Medulloblastoma	54	63	+	144	51	−	CSF response for 6 months; death due to progressive primary tumor
2	MOAA (GM)[a]	5	66	−	nd	nd	−	death due to primary tumor
3	Adenocarcinoma	38	51	+	61	88	+	no response
4	Anaplastic astrocytoma	140	61	−	82	61	−	abnormal myelogram remained stable
5	Melanoma	30	80	+	1400	37	+	no response
6	CUPS[b]	40	94	+	1561	100	+	no response
7	Medulloblastoma	980	44	−	1224	63	−	no response
8	Medulloblastoma	775	nd	+	162	nd	+	no response
9	Medulloblastoma	82	46	+	58	79	+	no response
10	CML blast crises	138	<10	+	50	3	+	no response
11	Glioblastoma	236	25	−	62	129	−	stable disease
12	Lung adenocarcinoma	300	<10	+	280	<10	+	no response
13	Glioblastoma	1438	32	+	nd	nd	−	initial response for 1 month, then expired before next evaluation
14	Ovarian cancer	62	52	+	124	54	+	no response
15	Medulloblastoma	nd	nd	+	nd	nd	−	initial response for 1 month, then failed
16	Primary CNS lymphoma	48	38	+	31	64	+	no response
17	Medulloblastoma	63	15	+	62	16	+	no response
18	Malignant ependymoma	57	9	+	67	16	−	response for 20+ months
19	ALL	23	56	+	32	69	−	response for 1 month
20	Oligodendroglioma	25	71	+	62	37	−	response for 2.5 months
21	Medulloblastoma	121	47	+	nd	nd	+	no response
22	Meningeal carcinomatosis	145	63	−	113	78	??	nonevaluable for CSF response due to shunt malfunction
23	Malignant ependymoma	110	nl	−	31	nl	−	„suspicious" lesion on myelogram that improved
24	Medulloblastoma	178	nd	−	204	nd	−	no response
25	Meningeal carcinomatosis	81	58	+	71	70	−	1+ month until LTFU
26	Gastric cancer			+			−	response for 3 months
27	HAA	nd	nd	+	nd	nd	?	patient expired prior to evaluation

[a] Transformed to GM
[b] Carcinoma, unknown primary site
Prot, protein; Glu, glucose; Cyt, cytology; nd, not done; +, positive; −, negative

gy, concurrent treatments, total dose of ACNU, and dose schedule. The total dose of ACNU varied between 9 and 104 mg, and the single dose range was 4–16.5 mg. For those patients who received what we considered to be a minimal course of ACNU (at least two doses) the dose range was 4–15 mg. In assessments of myelotoxicity, we did not observe any downward trend in WBC, platelets, or hematocrit (Hct) that could not be explained either by the sytemic tumor or by concomitant systemic chemotherapy (Table 2).

Of the 13 patients who received intrathecal administration (either lumbar or cervical taps), 3 (23%) developed transient radicular symptoms at a short distance from the injection site and 4 (31%) experienced local pain at the injection site. Of the 27 patients who received ACNU, 1 (4%) had severe nausea and vomiting in two of five treatments.

Direct CNS toxicity other than the radiculopathy and one case of nausea and vomiting appeared to be nonexistent. Although it is difficult at times to distinguish neurologic signs and symptoms due to meningeal neoplasia from drug effects on the CNS, it was the conclusion of neurologists examining the patients that there was no ACNU-induced CNS toxicity other than that cited above.

Antitumor activity

Table 3 summarizes the outcome of ACNU treatment with respect to CSF examination and clinical status. Of the 27 patients treated, 6 (22%) presented with negative cytology and other evidence of subarachnoid disease (stage 1); of this group of 6, 1 patient underwent a reduction in CSF protein and stabilized briefly (6 weeks). One additional patient had a "suspicious" myelogram prior to therapy that returned to normal following ACNU. Of the 21 (78%) patients with positive cytology (stages 2 and 3), 8 (38%) showed an improvement in cytology for 1–20+ (1, 1, 1, 1+, 2.5, 3, 6, 20+) months.

Of this group of CSF responders, one patient died of other causes after 1 month and one left the country. There were two patients who could not be evaluated for cytologic response: one died prior to a repeat CSF evaluation, and one patient with a shunt malfunction did not undergo a repeat cytology. There were four patients who were positive in both cytology and myelogram (stage 3): one died before evaluation and one responded in the CSF evaluation but left the country prior to a repeat myelogram (both previously described above); one failed to respond in either the CSF evaluation and or the repeat myelography; the final patient showed clearing of the CSF, but no response was seen by myelography. CSF protein levels did not always predict improvement; they went down clearly in two patients, clearly up in two, increased slightly (probably within experimental error) in two, and were not obtained in one.

Pharmacokinetics

Pharmacokinetic evaluations were attempted in the first 15 patients but were technically possible in only 13. Figure 2 shows the spinal CSF level of ACNU over time in patient 5 following an intrathecal injection of 5 mg. Table 4 summarizes the slow or beta-phase constants in eight patients studied by ventricular reservoir, one with lateral cervical puncture (LP sampling), and four from the L4–5 lumbar space after lumbar administration. The mean half-life was found to be 27 min, with B (μg/ml) varying from 19 to 194 μg/ml, depending on the dose and route of administration.

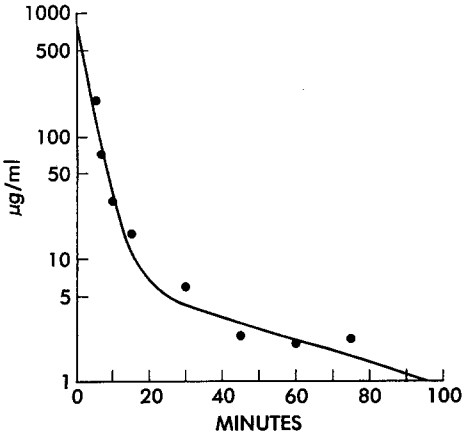

Fig. 2. CSF pharmacokinetics after intrathecal administration of 5 mg ACNU in patient 5. CSF samples were obtained from the lumbar puncture needle after barbotage. The curve was fit by a nonlinear iterative technique

Table 4. ACNU beta-phase constants from intraventricular CSF after reservoir injection

Patient number	Dose (mg)	Route[a]	B (μg/ml)	Beta (min^{-1})	$T_{1/2}$ (min)
2	4	L4-5	19.0	0.018	37.5
3	4	ventricular	19.0	0.027	26.1
4	8	L4-5	–		
5	5	L4-5	21.3	0.021	33.2
6	5	L4-5	25.0	0.047	14.7
7	5	ventricular	–		
8	10	C1-2 to L4-5	35.8	0.029	23.8
9	10	ventricular	30.9	0.029	23.8
10	10	ventricular	–		
11	10	ventricular	28.8	0.030	23.2
12	12	ventricular	20.8	0.029	24.2
13	12	ventricular	20.6	0.018	37.6
14	15	ventricular	194.0	0.032	21.3
Mean				0.028	27.0
± SD				0.008	7.4

[a] Route of injection and sampling was the same except in patient 8

The pharmacokinetics in 7 patients could be computed using the model-independent method of statistical moments to calculate the steady-state volume of distribution V_{ss}, the clearance, CL, the elimination constant, K_o, and the regional exposure integral (or area under the CSF curve) (Table 5). The V_{ss} varied from 24 to 101 ml and therefore was less than the expected total CSF volume; it could, however, reflect the limited CSF compartment accessible to the ACNU before it was cleared or degraded. The mean clearance was 3.8 ml/min (range, 1.0–6.2 ml/min). Peak ACNU levels varid between 108 and 620 μg/ml, with the AUC being 1.4–14.7 mg·min/ml.

Discussion

The major concerns of our preclinical pharmacokinetic and toxicity study in beagle dogs [13] were that intraventricular (and intrathecal) ACNU would be eliminated too rapidly from the CSF to distribute widely in the CSF and that local CNS toxicity would occur in humans to the same extent as in the dogs. The half-life of ACNU in pH 7.4 phosphate buffer is 33 min and in plasma, 29 min [10]. It was somewhat faster in the present CSF studies: ACNU elimination from the ventricular CSF had a beta slope of 0.028 min^{-1} (27 min) and a computed K_o of 13 min. In two cases where an LP was done after intraventricular administration of ACNU, we could not measure ACNU (< 0.01 μg/ml) in lumbar fluid between 1 and 3 h after ventricular administration.

Although it is very difficult to study the CNS toxicity of drugs injected into the CSF for meningeal neoplasia unless the toxicity is quite different from that produced by the disease itself, as it is with methotrexate, our impression is that ACNU doses as high as 15 mg and total doses of 75–104 mg were well tolerated.

Table 5. ACNU CSF pharmacokinetics

Patient number	Dose (mg)	Route	Peak (μg/ml)	V_{ss} (ml)	Cl (ml/min)	K_o (min^{-1})	AUC (μg · min/ml)
3	4	ventricular	306	25.3	1.4	0.0565	2,803
9	10	ventricular	108	91.0	5.1	0.0559	1,965
11	10	ventricular	260	101.5	6.2	0.0611	2,407
12	12	ventricular	542	56.1	3.9	0.0695	3,360
14	15	ventricular	620	23.8	1.0	0.0430	14,679
5	5	L4-5	393	73.9	2.5	0.0333	2,033
6	5	L4-5	200	94.8	3.5	0.0368	1,433
Mean					3.8	0.0521	
± SD					1.6	0.0129	

It is also difficult to be certain of the efficacy of a drug in a heterogeneous group of patients with varying causes and degrees of meningeal neoplasia. Of 21 patients, 8 with positive cytology converted their cytology to negative and either stabilized or responded for periods of 1 to 20+ months. Since this was not a randomized study comparing ACNU with another agent, it is impossible to tell whether its efficacy is comparable to that of methotrexate, cytosine arabinoside, or thio-TEPA. However, based on the extremely rapid CSF elimination of ACNU, it is not likely that ACNU will widely distribute from the site of administration. For instance, using the data from Table 4, let us assume a slow phase intercept, B, of 20 μg/ml and a slope, beta, of 0.028 min^{-1}. At 3 h, the CSF level would be 0.1 μg/ml, a value too low to have a therapeutic impact if it represents CSF ACNU that has just reached the convexity or lumbar subarachnoid space.

It is likely that this and other cytotoxic agents that can be given into the CSF for meningeal neplasia should be injected by a short-term ventricular-to-lumbar infusion, which would provide a very rapid attainment of high CSF drug levels in the entire ventricle-to-lumbar-theca axis. The potential for therapeutic levels at more distant sites such as the basal cisterns and convexity subarachnoid would thus be more likely. Such an approach has been instituted in Japan (Y. Ushio, personal communication, 1987), with high ACNU levels in both ventricular and lumbar CSF, no obvious neurotoxicity, and some therapeutic efficacy. We would strongly support that approach with drugs such as ACNU.

References

1. Band PR, Holland JF, Bernard J, Weil M, Walker M, Rall D (1973) Treatment of central nervous system leukemia with intrathecal cystosine arabinoside. Cancer 32: 744–748
2. Benet LZ, Galeazzi RL (1979) Noncompartmental determination of the steady-state volume of distribution. J Pharm Sci 68: 1071–1074
3. Bleyer WA (1978) Current status of intrathecal chemotherapy for human meningeal neoplasms. Natl Cancer Inst Monogr 46: 171–178
4. Chan KK, Gibaldi M (1982) Estimation of statistical moments and steady-state volume of distribution for a drug given by intravenous infusion. J Pharmacokin Biopharm 10: 551–558
5. Davson H (1967) Physiology of the cerebrospinal fluid. Churchill, London, p 4
6. Fulton DS, Levin VA, Gutin PH, Edwards MS, Seager ML, Stewart J, Wilson CB (1982) Intrathecal cystosine arabinoside for the treatment of meningeal metastases from malignant brain tumors and systemic tumors. Cancer Chemother Pharmacol 8: 285–291
7. Gutin PH, Levi JA, Wiernik PH, Walker MD (1977) Treatment of malignant meningeal disease with intrathecal thio-TEPA: a Phase II study. Cancer Treat Rep 61: 885
8. Hustu HO, Aur RJA, Verzosa MS, Simone JV, Pinkel D (1973) Prevention of central nervous system leukemia by irradiation. Cancer 35: 585–597
9. Hyman CB, Bogle JM, Brubaker CA, Williams K, Hammond D (1965) Central nervous system involvement by leukemia in children: II. Therapy with intrathecal methotrexate. Blood 25: 13–22
10. Levin VA (1981) Clinical pharmacology of the nitrosoureas. In: Prestayko AW, Crooke ST, Baker LH, Carter SK, Schein PS (eds) Nitrosoureas. Academic Press, New York, pp 171–180
11. Levin VA, Wilson CB, Crafts D, Norman D, Holler P, Spire JP (1977) Criteria for evaluating malignant brain tumor patients undergoing chemotherapy. J Neurosurg 47: 329–335
12. Levin VA, Csejtey J, Byrd DJ (1983) Brain, CSF, and tumor pharmacokinetics of alpha-difluoromethylornithine in rats and dogs. Cancer Chemother Pharmacol 10: 196–199
13. Levin VA, Byrd D, Campbell J, Giannini DD, Borcich JK, Davis RL (1985) CNS toxicity and CSF pharmacokinetics of intraventricular ACNU and other nitrosoureas in beagle dogs. Cancer Res 45: 3803–3809
14. Shapiro WR, Posner JB, Ushio Y, Chernik NL, Young DF (1977) Treatment of meningeal neoplasms. Cancer Treat Rep 61: 733
15. Wang JJ, Pratt CB (1970) Intrathecal arabinosyl cystosine in meningeal leukemia. Cancer 25: 531–534

Received June 9, 1988/Accepted September 16, 1988