Phase 2 study of idarubicin in pediatric brain tumors: Pediatric Oncology Group study POG 9237

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Idarubicin (IDA), the 4-demethoxy analog of daunomycin, has had significant cytotoxicity in many malignancies. In previous reports, the alcohol metabolite of IDA, 4-demethoxydaunorubicinol (idarubicinol, or IDOL), had cytotoxic activity and the ability to penetrate the blood-brain barrier. For this reason, the Pediatric Oncology Group conducted a Phase 2 trial of IDA for children with recurrent or progressive brain tumors. Ninety-one eligible children were entered on this study, with ages ranging from 3 months to 19 years. Patients were stratified by tumor types into 6 categories: stratum 1, low-grade astrocytoma; stratum 2, malignant glioma (glioblastoma multiforme and anaplastic astrocytoma); stratum 3, medulloblastoma; stratum 4, brainstem glioma; stratum 5, ependymoma; and stratum 6, miscellaneous malignant tumors not included in the previous diagnoses. IDA (18 mg/m^2) was infused over 4 h and followed by granulocyte colony-stimulating factor (G-CSF) beginning day 5 after infusion of IDA. G-CSF was continued until blood cell count recovery. Cycles were repeated at approximately 21-day intervals until patients developed progressive disease or had completed 6 cycles with stable or improved disease. Pharmacokinetic plasma and cerebrospinal fluid (CSF) samples were collected from a subset of these patients. Response was poor in all strata. Most patients developed progressive disease; however, in 21 patients with medulloblastoma there was 1 partial response, and 6 patients had stable disease (SD) that in 4 patients lasted more than 20 weeks. Grades 3/4 hematopoietic toxicities were the most common toxic events, and 14 infection-related events resulted in hospitalization of patients. Only 1 patient developed reduced cardiac function. The systemic clearance data for IDA and IDOL were nearly identical to those published on patients with leukemia, and the plasma elimination of the IDOL metabolite was substantially longer than that of the parent drug IDA. The peak CSF:plasma ratios of IDA and IDOL were very low. The

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[2] Abbreviations used are as follows: CR, complete response; CSF, cerebrospinal fluid; G-CSF, granulocyte colony-stimulating factor; IDA, idarubicin; IDOL, 4-demethoxydaunorubicinol (idarubicinol); PD, progressive disease; PFI, progression-free interval; PR, partial response; SD, stable disease.

overall response rates to IDA were disappointing despite periods of prolonged SD in nearly a fourth of the patients. We conclude from this data and from that in nonhuman primates that it is unlikely that IDA, daunomycin, or other related anthracyclines will be useful for treating primary CNS tumors. *Neuro-Oncology 5, 261–267, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-056, August 00, 2003. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152 8517 02 00056 X)*

Idarubicin (IDA)[2] is the 4-demethoxy analog of daunomycin, suggested to have significant cytotoxicity against many adult and pediatric leukemias and solid tumors. Unlike other anthracyclines, the alcohol metabolite of IDA, 4-demethoxydaunorubicinol (idarubicinol, or IDOL), also possesses significant cytotoxic activity. The drug is eliminated predominantly in the IDOL form by biliary and, to a lesser extent, renal excretion, with a terminal half-life that exceeds 45 h. Phase 1/2 studies of IDA revealed that myelosuppression and mucositis are dose-limiting toxicities (Tan et al., 1987).

Data is limited regarding in vitro/in vivo activity of lipophilic anthracyclines in CNS tumors. In vitro, IDA inhibits growth and DNA synthesis in rat C6 glioblastoma cells better than daunorubicin and doxorubicin (Schott and Robert, 1989). No studies have been done with IDA in vivo in a CNS tumor model; however, a lipophilic anthracycline similar to IDA, MX2 (3'deamino-3'morpholino-13 deoxy-10 hydroxycarcinomycin), had in vivo activity with 20% to 40% longer survival in a rat leptomeningeal tumor model (Izumoto et al., 1990). More lipophilic than its parent compound daunomycin, IDA uncommonly produces measurable levels in cerebrospinal fluid (CSF). In contrast, its metabolite IDOL has penetrated the blood-brain barrier, producing CSF concentrations near those reported as cytotoxic to human tumor cell lines (≥0.5–1 ng/ml) after treatment with intravenous doses of ≥10 mg/m^2 of IDA (Reid et al., 1990; Speth et al., 1989).

With this background, a Phase 2 trial of idarubicin that included pediatric patients who had recurrent or progressive brain tumors was conducted by the Pediatric Oncology Group to determine efficacy of IDA, establish its hematologic toxicity when administered with granulocyte colony-stimulating factor (G-CSF) support, and investigate CSF and plasma pharmacokinetics of IDA and IDOL.

Materials and Methods

Patient Eligibility

Eligible patients were under 21 years old and had biopsy-proven diagnoses of primary malignant intracranial or spinal cord tumors that were recurrent or progressive after conventional radiotherapy or chemotherapy. Histologic confirmation was required for all patients except those with deep midline or brainstem tumors. Biopsies were encouraged strongly to rule out radiation necrosis causing radiographic progression after hyperfractionated radiation in patients with brainstem tumors. Eligible patients had disease measurable by MRI scan or CT scan or had tumor cells in their CSF. They were recovered from toxic effects of any chemotherapy and 12 weeks past radiation therapy. Patients were ineligible if they had cumulative anthracycline doses of ≥250 mg/m^2 of doxorubicin or ≥350 mg/m^2 of daunorubicin. Normal cardiac function, defined as left ventricular shortening fraction of >29% or resting ejection fraction of >55%, was also required for entry. Continuation of dexamethasone therapy to eligible patients was allowed as long as the dose was not escalated. Before therapy began, patients' marrow had to recover to normal hematopoietic function (absolute neutrophil count ≥ 1500/mm^3 and platelet count ≥ 100,000/mm^3). Patients also needed adequate renal function (creatinine < 2.0 mg/dl) and hepatic function (bilirubin < 1.5 times the institutional normal). Patients were eligible who had recovered from autologous bone marrow transplantation. All patients or their legal guardians were required to sign informed consent consistent with federal and local guidelines and the Declaration of Helsinki.

Patients' tumors were stratified into 6 tumor categories as specified in the protocol. Table 1 shows the number of tumors in each category: stratum 1, astrocytoma; stratum 2, malignant glioma (anaplastic astrocytoma, glioblastoma multiforme, and other WHO grade III/IV astrocytomas); stratum 3, medulloblastoma; stratum 4, brainstem glioma; stratum 5, ependymoma; and stratum 6, miscellaneous malignant brain tumors not included with the previous diagnoses.

The study was designed to detect an objective response rate (complete plus partial response) of at least 30% with an 87% probability. The study would stop early if the objective response rate in the stratum was too low and would continue to the full accrual of 25 patients otherwise. Patient accrual was determined by Gehan's recommendations for phase 2 studies (Gehan, 1961).

Chemotherapy

The chemotherapy regimen was based on phase 1/2 study data. IDA (18 mg/m^2) was infused over 4 h every 21 days or as soon thereafter as patients' blood-cell counts recovered (Daghestani et al., 1985). G-CSF was given on day 5 of each course of IDA because of the prolonged plasma half-life of IDOL (50 h). We believe that in vivo activity of IDA in CNS tumors may be related to IDOL, so we chose a dose schedule of IDA to achieve peak IDOL levels, a single daily regimen of 18 mg/m^2 as a 4-h infusion. The dose was repeated at 21-day intervals or as soon as patients' blood counts recovered. Beginning day 5 of each cycle, a subcutaneous injection of G-CSF 5 μg/kg was administered daily and continued until an absolute neutrophil count of 1000 was reached after nadir. Appropriate blood-product support was provided to patients with platelet counts of <40,000/mm^3 or hemoglobin <7.5 g/dl. IDA dose was reduced by 20% in patients who needed >28 days for hematopoietic recovery.

Pharmacokinetic Sampling

Pharmacokinetic studies were performed with a subset of enrolled patients. Plasma sample points were 0.25, 1, 2, 4, 8, 12, 24, and 36 h after the end of 4-h IDA infusion. When clinically feasible, CSF samples were collected from ventricular reservoirs at 4, 8, 12, 24, and 36 h after the end of idarubicin infusion. Plasma and CSF samples were frozen and stored at –70°C until assayed. IDA and IDOL plasma and CSF concentrations were quantitated with an HPLC assay (de Graff et al., 1989).

Evaluation Criteria

Disease evaluations using CT or MRI were done after the second and fourth courses of treatment or at the time of clinical disease progression. Patients with positive CSF cytologies also had repeat cytologic assessments during their evaluations. For patients who showed objective responses or stable disease (SD), subsequent scanning was done after every third cycle.

Response was defined by calculating the product of the largest 2 cross-sectional diameters of the patient's tumor before and after treatment. Complete response (CR) was defined as total disappearance of radiographically discernable disease. Three consecutive negative spinal taps at least 2 weeks apart were required for patients whose only diagnostic confirmation of disease was positive CSF cytology at study entry. A patient had a partial response (PR) if there was at least a 50% reduction in the product of the cross-sectional tumor diameters. CSF cytologic responses were defined as in patients with initially positive CSF cytology who had at least 2 subsequent negative CSF examinations at least 2 weeks apart. Stable disease was defined as less than 50% reduction in tumor size and no evidence of clinical progression. Progressive disease (PD) was defined as positive CSF in cases of initially negative CSF, >25% increase in known measurable disease, appearance of a new radiographically detectable intradural tumor, or SD with neurologic deterioration from tumor progression. Progression-free intervals (PFIs) were calculated from the date of study entry until the date of recurrence or progression.

The protocol recommended that patients whose condition was at least SD continue therapy until at least 6 cycles were completed. Patients who had CR or PR were required to submit scans for central review.

Cardiac toxicity was monitored by baseline cardiac evaluation, including EKG and either shortening fraction or ejection fraction at study entry. Cardiac evaluations were repeated after second and fourth courses of therapy, then every 3 cycles with continued IDA therapy.

Off-Study Criteria

Patients were removed from study if there was evidence of progressive or recurrent disease by radiographic imaging or positive CSF cytology any time after completion of at least 1 cycle of therapy. Reduction of shortening fraction to <27% or ejection fraction to <50%, development of cardiac arrhythmia, or increase in creatinine or total bilirubin >100% over baseline also resulted in the patient's removal from study.

Results

Between May 1992 and May 1995, 92 children were entered. One was declared ineligible after initial study entry because of abnormal cardiac function on screening examination prior to beginning therapy. Information on this patient is not included in this report. The range of ages at diagnosis for eligible children was 3 months to 19 years. All histology samples were centrally reviewed. Patients for whom diagnostic material was inadequate were assessable for toxicity only. Table 1 shows the characteristics of our cohort. Patients had received many different therapies, including surgery, chemotherapy, conventional radiotherapy, and radiosurgery. Eight patients had undergone ablative chemotherapy followed by marrow rescue.

Eighty of 91 patients were assessable for response to treatment. Eleven patients were not assessable for response because they died <16 days from treatment start date (n = 9) or had inadequate response data (n = 2). Eighty-six of 91 patients were assessable for toxicity, which was graded according to the NCI Common Toxicity Criteria (NCI, 1993).

Response

Responses to treatment are summarized in Table 2. Among the 8 stratum 1 patients (astrocytoma), 2 had stable disease, 1 for 11 weeks and the other for 129 weeks. Five had PD, 1 in the first cycle and 4 during the second or later cycle. One patient died early from PD.

Among 18 patients with malignant glioma, 1 patient achieved a PR and after completing 6 cycles of IDA went on to autologous marrow transplantation (PFI 29 weeks).

Table 1. Patient characteristics and diagnoses by tumor type

Characteristic	Number
Eligible patients*	91
Males/Females	50/41
Prior Therapy	
Chemotherapy and radiation only	70
Chemotherapy, radiation, and ABMT	8
Radiation alone	10
Chemotherapy alone	3
Number assessable for toxicity	86/91
Diagnosis (stratum)	
(1) Astrocytoma	8
(2) Malignant glioma	18
(3) Medulloblastoma	21
(4) Brainstem glioma	10
(5) Ependymoma	15
(6) Other	19

Abbreviation: ABMT, autologous bone marrow transplantation.

* Age range, 3 months–19 years; median, 6.5 years.

Table 2. Response rates*# and duration (weeks) for eligible patients

Diagnosis	n	PR	SD	PD
1. Astrocytoma	8	0	2 (11–29)	5
2. Malignant glioma	18	1 (154)	3 (10–309)	13
3. Medulloblastoma	21	1 (12)	6 (3–292)	11
4. Brainstem glioma	10	0	1 (9)	7
5. Ependymoma	15	0	4 (13–270)	8
6. Other	19	1 (18)	2 (19–22)	15
Total	91	3	18	59

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

*Unable to assess response in 11 patients: early death (9); response unknown (2).

#There were no complete responses.

The patient subsequently remained in CR more than 2 years before recurrence. Three others had prolonged SD from 10 to 309 weeks. Another patient died early from PD.

Among the 21 medulloblastoma patients, 1 achieved a PR, 6 had SD with PFIs of 3 to 292 weeks, and 11 had progression within 2 cycles of therapy. Two patients died early from PD and 1 patient died from sepsis.

One of 10 stratum 4 (brainstem glioma) patients had a brief PFI of 9 weeks, whereas 7 had rapid progression after 1 or 2 cycles of IDA. One of the stratum 4 patients died early from PD, and another from sepsis.

Among 15 patients in the ependymoma stratum, 4 achieved PFIs ranging from 13 to 270 weeks, 8 had rapid progression, 2 died early from PD, and response was unknown for 1 patient .

Nineteen patients were registered on stratum 6 with miscellaneous tumors including rhabdoid tumor (5), pineoblastoma (2), germinoma (2), choroid plexus carcinoma (1), choroid plexus papilloma (2), pineocytoma (1), ependymoblastoma (1), and other (5). Of those with rhabdoid tumors, 3 were originally entered on study as having medulloblastoma, but following central pathologic review, the diagnosis was revised. One patient with a rhabdoid tumor achieved a PR within 2 cycles but developed progression 18 weeks later after the third cycle. One patient with neuroblastoma and 1 patient with choroid plexus carcinoma had SD, with PFIs of 19 and 22 weeks, respectively. The remaining patients' diseases progressed within 2 cycles of therapy.

Toxicity

As shown in Table 1, nearly all patients on this protocol were pretreated heavily. With the exception of 10 who were treated with radiotherapy alone and 3 who received chemotherapy alone, all other patients had received multimodal treatment including chemotherapy and radiotherapy. The primary toxicity event associated with the current study was grade 3/4 hematopoietic toxicity, and 71 of the 86 patients who were assessable for toxicity had grade 3 or 4 neutropenia. There were 14 infection-related events, which resulted in admission to the hospital. Of those, fever without source was most common, while 3 patients were diagnosed with sepsis, 1 with unspecified pneumonia, and 1 with *Varicella*. There were 2 toxic deaths related to sepsis. One patient who did not receive G-CSF died from gram-positive bacterial sepsis, and another who did receive G-CSF died from gram-negative bacterial sepsis. One patient had a lung abscess that was presumed to have been caused by *Nocardia*.

Grade 3/4 thrombocytopenia was seen in 48 of 86 patients. Minor hemorrhagic complications were noted incidentally in scans of 2 patients who had evidence of tumor progression. In 1 patient who had a seizure, MRI showed evidence of PD with temporal lobe hemorrhage.

Twenty-three cycles of therapy were given to 8 patients who had previous ablative chemotherapy followed by bone marrow rescue. The hematopoietic toxicity in that group was comparable to that in other patients.

All patients had normal cardiac function at entry. No patients had been exposed to anthracyclines, although several had received cyclophosphamide at varying doses. Most had received craniospinal radiation, except those with brainstem gliomas. One patient, who had previously undergone an autologous marrow transplantation and received craniospinal radiotherapy, had a minor drop in cardiac ejection fraction to 48% after receiving 10 cycles of therapy without experiencing clinical symptoms or requiring cardiac medications. The patient was subsequently removed from study. Five others who received ⩾6 cycles of IDA maintained normal serial cardiac function.

Only 1 patient had stomatitis, a dose-limiting toxicity in adult studies (Daghestani et al., 1985; Tan et al., 1987). One patient who had a history of renal dysfunction but normal function at the time of entry had a rise in creatinine to 2.4 mg/dl after 1 cycle of therapy. He was removed from study because of PD at that time.

Pharmacokinetic Analysis

Pharmacokinetic studies were completed during the first IDA course in 14 patients (median age 7.2 years, range 2.2–19 years). Clinical diagnoses were representative of all patients: astrocytoma, 2; malignant glioma, 1; medulloblastoma, 6; brainstem glioma, 1; ependymoma, 1; pineoblastoma, 1; rhabdoid tumor, 1; neuroblastoma, 1. Depicted in Fig. 1 are the mean plasma concentrations and a best-fit disposition curve for IDA. Also shown is the plasma concentration data for IDOL and the simultaneous CSF levels of the parent IDA and the IDOL alcohol metabolite. The plasma clearance for IDA was 38 l/h/m^2, with a terminal half-life of 13 h. IDOL clearance was not calculated, but its elimination half-life was 50 h. The ventricular and lumbar CSF concentrations and CSF:plasma ratios in 11 patients are shown in Table 3 according to times at which samples were collected.

Among 9 children studied, sample collection included single lumbar (n = 4) or multiple (2–4 serial samples) ventricular (n = 5) CSF samples for IDA and IDOL measurement. In CSF, IDA and IDOL were present at the first time point measured (4 h after infusion). The CSF dispositions of both compounds mirrored those in plasma. Although the number of lumbar samples was small, the concentrations did not appear to differ significantly in

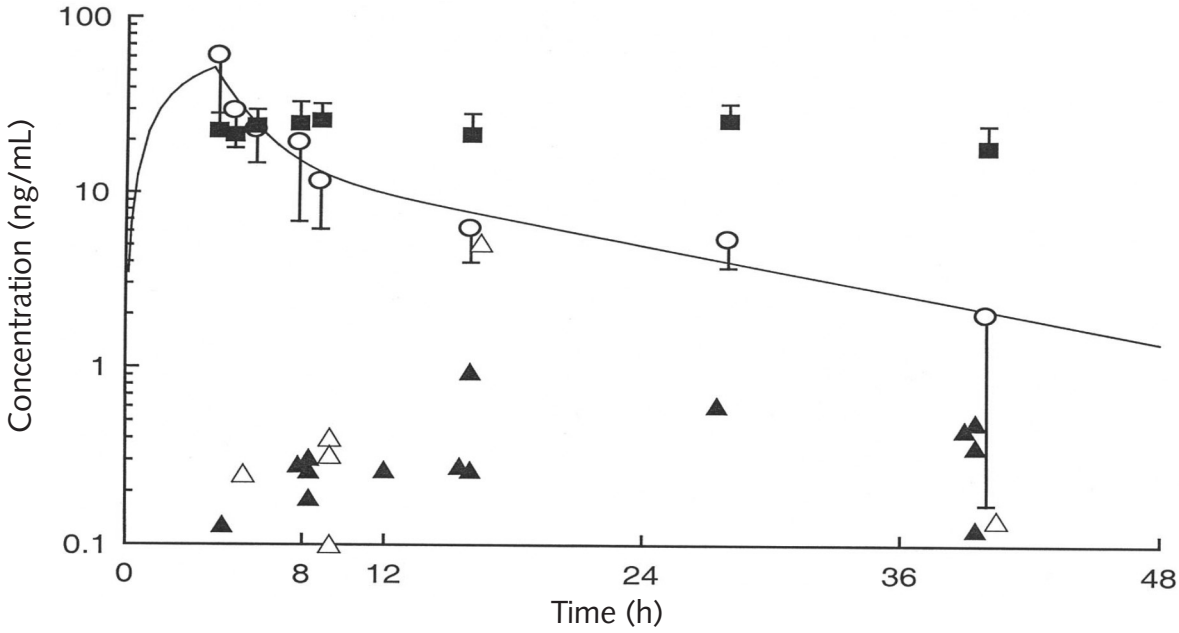

Fig. 1. Mean plasma and CSF concentrations for IDA and IDOL after start of 4-h (18-mg/m^2) IDA infusion. Open circles represent the mean plasma IDA concentrations. The solid line represents the model-generated disposition curve. Vertical bars represent half the range associated with each point. Closed boxes represent mean plasma IDOL concentrations; the vertical bars represent half the range associated with each point. Open and closed triangles represent individual CSF IDA and IDOL concentrations, respectively, from patients studied at corresponding time points on the horizontal axis.

Table 3. Ventricular and lumbar CSF concentrations (ng/ml) for IDA and IDOL and CSF:plasma ratios for 11 separate patients at specified time points*

		Ventricular Levels (CSF:plasma ratio)		Lumbar Levels (CSF:plasma ratio)	
Sampling Time (h)	Patient	IDA	IDOL	IDA	IDOL
1	1	0.24	0.13	—	—
4	1	0.32	.31	—	—
	2	0.04 (0.017)	0.34 (0.01)	—	—
	3	ND	0.26	—	—
	4	ND	0.42	—	—
	5	0.1	0.2	—	—
	6	ND	0.13 (0.05)	—	—
8	2	ND	0.26 (0.008)	—	—
	4	ND	0.3	—	—
	7	—	—	ND	0.33
12	2	ND	0.26	—	—
	3	ND	0.29	—	—
	4	ND	0.41	—	—
	8	—	—	5.2	0.95
24	9	—	—	0	0.62
36	3	ND	0.13	—	—
	5	ND	0.36	—	—
	10	—	—	ND	0.5
	11	—	—	0.14	0.46

Abbreviation: ND, not detectable.

*—, sample not obtained.

ventricular and lumbar spaces (Table 3). Two patients (patients 2 and 6) had plasma and CSF levels measured simultaneously. Patient 2 had a 0.017 IDA CSF:plasma ratio at 4 h with no detectable CSF levels at 8 and 12 h. IDOL CSF:plasma ratios in the same patient were 0.01, 0.008, and 0.0 at 4, 8, and 12 h, respectively, after infusion. Patient 6 had no detectable IDA in CSF at 4 h, but the IDOL CSF:plasma ratio was 0.05. Patient 8 had levels of the parent drug and metabolite well beyond the mean for the group and had no plasma data available for comparison.

Discussion

Anthracyclines had not been studied in any clinically meaningful trials in childhood brain tumors prior to this study. The lipophilicity of IDA and the cytotoxicity and good CNS penetration reported for its alcohol metabolite, IDOL, suggested that IDA was a reasonable agent to investigate in recurrent CNS tumors. To our knowledge this is the first prospective clinical and pharmacokinetic evaluation of IDA in CNS tumors.

No significant clinical activity of IDA using the prescribed dose and schedule was found. Only 3 of 91 patients had objective responses, and no patient achieved a CR. Eighteen of 91 had SD with PFIs greater than 20 weeks (most common in patients with medulloblastoma [n = 4]), suggesting the potential for some limited antineoplastic activity. Comparison of the above results with other phase 2 studies of IDA revealed generally similar results, with the possible exception of a higher rate of

objective responses in malignant gliomas. Among 75 pediatric patients with recurrent CNS tumors reported by Arndt et al. (1998) using IDA in a daily dose of 5 mg/m^2 × 3 days every 3 weeks, responses were rare for tumor categories other than malignant gliomas; 2 of 19 such patients had PRs, and 1 had a CR. Similar results were reported in adult malignant gliomas by Bushunow et al. (1998). Using the same dose and schedule of IDA reported here, those authors observed 2 PRs and 5 SDs of 15 to 40 weeks' duration among 30 adults with recurrent malignant gliomas (Bushunow et al., 1998).

Nine of 91 eligible patients experienced early deaths, of which 7 were due to disease progression. Despite an eligibility requirement that patients have an estimated life span of 8 weeks, this high number of deaths from PD would suggest that these patients were nearer end stage than was appreciable medically at the time of study entry. Two additional patients had infection-related early deaths.

As anticipated, grade 3/4 myelosuppression was the most common toxicity reported. Despite that, only 20% of patients needed hospitalization for fever and neutropenia, and only half had bacteremia. However, 2 fatal events were related to bacterial sepsis, 1 occurring in a patient who did not receive G-CSF. The potential effect of G-CSF on minimizing infection-related toxicity is uncertain. There is no comparable data from similar populations who did not have G-CSF support.

Despite the history of frequent use of cyclophosphamide and spinal radiation for treatment within our patient cohort, there was no significant cardiac toxicity observed in this study. One patient did have a minor drop in cardiac ejection fraction but did not require medical intervention.

The systemic clearance we observed for IDA and the terminal half-life for IDA and IDOL observed here were nearly identical to those reported by Reid et al. (clearance of 41 l/h/m^2) in patients with acute leukemia (Reid et al., 1990). Consistent with the observations of those authors, we noted that plasma elimination time for the IDOL metabolite was substantially longer than that for the parent drug, as shown in Fig. 1.

The peak CSF:plasma ratios of IDA and IDOL were very low. Although there is no similar serially obtained human CSF data with which to compare these results, data from studies in nonhuman primates suggest that human penetration of IDA and IDOL may be lower. After an 8-mg/kg bolus dose of IDA in 3 animals (Berg et al., 1999), single time point CSF:plasma ratios for IDA (0%, 8%, and 15%) and IDOL (2%) appear to be higher than those noted here (Arndt et al., 1998). Our data and that from the nonhuman primate study show CSF IDA and IDOL levels that are markedly lower than would be predicted from the single time point CSF analyses reported by Reid et al. (1990).

These data suggest that penetration of the parent drug and metabolite is very low. Peak concentrations of IDA and IDOL were well below the inhibitory concentration, at which 50% of cells are killed, of 2.4 ng/ml and 0.9 ng/ml, respectively, for malignant glioma and leukemia cell lines in vitro, in all but 1 patient listed in Table 3. These data and the nonhuman primate data indicate that it is unlikely that IDA, daunorubicin, or the other anthracyclines will be useful compounds for treating primary CNS tumors (Berg et al., 1999; Kuffel et al., 1992).

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