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Cerebrospinal fluid pharmacokinetics of carboplatin in children with brain tumors*

R. Riccardi[1], A. Riccardi[1], C. Di Rocco[2], G. Carelli[3], R. L. Tartaglia[1], A. Lasorella[1], T. Servidei[1], and R. Mastrangelo[1]

[1] Division of Pediatric Oncology, [2] Section of Pediatric Neurosurgery, [3] Department of Occupational Medicine, Catholic University of Rome, Italy

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Summary. The pharmacokinetics of carboplatin in cerebrospinal fluid (CSF) and plasma was studied in five children with brain tumors (four medulloblastomas and one ependimoblastoma) who underwent preirradiation treatment with carboplatin. Carboplatin pharmacokinetics was studied following the administration of 600 mg/m^2 as a 1-h infusion. Four children were treated a few weeks after surgery, whereas one child with an unresectable tumor was treated prior to surgery. All patients had a ventricular-peritoneal CSF shunt connected to a subcutaneous reservoir. Total platinum and free carboplatin were measured. The mean AUC values for free carboplatin in CSF and plasma were 2.29 ± 1.20 and 8.18 ± 1.27 mg ml^{-1} min, respectively. The mean ratio of CSF AUC to plasma AUC was 0.28 (range, 0.17–0.46). Both plasma peak levels and AUC values showed limited interpatient variability. On the other hand, carboplatin levels in CSF showed substantial interpatient variability, with a >5-fold difference in peak levels and a 3-fold difference in AUC values being recorded. The interpatient difference in CSF pharmacokinetics may have been related at least in part to the different anatomical alterations induced by the surgical procedures or by the presence of a large tumor mass. In the four evaluable patients exhibiting macroscopic residual tumor, we observed one complete remission (CR) and two partial remissions (PR) following two cycles that consisted of two doses of 600 mg/m^2 carboplatin given on 2 consecutive days (total dose, 1200 mg/m^2) and were separated by a 1-month interval. These results may give some indication as to the optimal dose and schedule for carboplatin administration in the treatment of primitive neuroectodermic tumors (PNET).

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Offprint requests to: R. Riccardi, Division of Pediatric Oncology, Catholic University, L. go Gemelli, 8, I-00168 Rome, Italy

Introduction

Cisplatin (CDDP) is an antineoplastic agent that is very effective against cancer in both adults and children. The therapeutic potential of cisplatin has been somewhat limited by its major toxic effects, namely, renal damage, ototoxicity, and severe nausea and vomiting. Because of its favorable therapeutic index, carboplatin is the most promising CDDP analogue. Since 1981, several phase I studies have been conducted in adult patients using carboplatin given on different schedules. The results have confirmed the preclinical findings of low renal and neurologic toxicity along with substantial but reversible myelotoxicity. The activity of carboplatin has also been evaluated in patients with different types of cancer, showing a spectrum of antitumor activity comparable with that of CDDP. In subsequent phase I–II studies in children, carboplatin has been found to be effective against brain tumors [1, 6], producing objective response rates (CR + PR) of 32% in relapsed patients with medulloblastoma (Med) and 14% in ependimoblastoma (Ep) [6]. Although 560 mg/m^2 given once monthly and 175 mg/m^2 given once weekly $\times 4$ were the schedules and doses suggested for phase II studies, it soon became evident that higher doses could be reasonably tolerated by adult patients [8].

Although the blood-brain barrier (BBB) is not completely intact in persons with brain tumors, it nonetheless plays a role in limiting the amount of drug that is delivered to brain-tumor cells in some areas [2]. The concentrations of systemically delivered drug in the cerebrospinal fluid indicate the amount of drug that crosses the BBB to reach the extracellular space in the brain. In the present study, we evaluated the CSF pharmacokinetics of carboplatin in five children with brain tumors. The patients received high-dose carboplatin, with 600 mg/m^2 being given for 2 consecutive days as a 1-h infusion. Plasma and CSF levels were measured during the first 24 h of treatment; thus, our observations refer to the systemic administration of 600 mg/m^2 carboplatin.

Table 1. Patients' characteristics

Case	Patient	Age (years)	Histology	Previous treatment	Disease at time of treatment
1	O. B.	6	Med	Surgery	Recurrence in the frontal lobe and posterior fossa
2	L. W.	7	Med	Surgery	Completely resected, spinal metastases
3	D. S. D.	3.5	Ep	Surgery	Partially resected
4	L. R.	7	Med	Surgery	Completely resected
5	M. S.	1.5	Med	None	Large tumor in the posterior fossa

Patients and methods

Patients. Five children with brain tumors (four Meds and one Ep) who received carboplatin were studied; their characteristics are shown in Table 1. Patient 1 had undergone surgery alone in another institution following an erroneous diagnosis of astrocytoma; 1 year later, she was referred to our center with frontal metastasis measuring 8 cm in diameter and tumor recurrence in the posterior cranial fossa. Patient 5, an 18-month-old girl, was treated with carboplatin prior to surgery. The pharmacokinetics study was performed only during the 1st day of treatment to avoid excessive CSF sampling. All children exhibited normal hepatic and renal functions, i.e., blood urea nitrogen (BUN) levels of <20 mg/100 ml, creatinine values of <1.5 mg/100 ml, and creatinine clearance of >70 ml min^{-1} 1.73 m^2. The creatinine clearances for patients 1, 2, 3, 4, and 5 were 81, 90, 95, 87, and 102 ml min^{-1} 1.73 m^2, respectively. Informed consent was obtained from members of all patients' families.

Sampling. Carboplatin vials (lyophilized, 150 mg/vial with 150 mg mannitol) were reconstituted with 100 ml 0.9% NaCl solution and then infused over 1 h. Plasma samples were obtained at baseline, at the end of the infusion, and at 1, 2, 4, 6, 8, 12, and 24 h after the end of the infusion. CSF samples were obtained at baseline, at the end of the infusion, and at 6 and 24 h after the infusion (a 2-h CSF sample was also obtained from the last three patients studied). All patients had a ventricular-peritoneal CSF shunt connected to a subcutaneous reservoir, which enabled repeated sampling of ventricular CSF. The mean opening pressure of the CSF shunt was the same in all children. At the moment of the examination, the hydrocephalus appeared to be controlled in all cases.

Carboplatin assay. Blood samples were immediately placed on ice and then centrifuged at 1000 *g* for 10 min to separate the plasma. Plasma and CSF were frozen at –70° C until carboplatin analysis, which was performed within 1 week. Plasma ultrafiltrate (UF) was obtained by centrifugation at 1500 *g* for 30 min using an Amicon MPSI Micropartition System (cutoff, 10,000 Da). Free drug in the plasma and CSF was measured by the high-performance liquid chromatographic (HPLC) assay described by Gaver et al. (limit of detection, 0.5 µg/ml [5]. The intra- and interassay CV values were 2% ($n = 8$) and 5% ($n = 10$), respectively, at a concentration of 25 µg/ml. Flameless atomic absorption spectrophotometry was used to assay total platinum and UF samples under the detection limit of the HPLC procedure; the method of El-Yazigi and Al-Saleh [4] was used, with slight modifications being made in the thermal program (limit of detection, 0.02 µg/ml). The intra- and interassay CV values were 2% ($n = 7$) and 3.5% ($n = 5$), respectively.

Pharmacokinetic analysis. The plasma and CSF AUC values were calculated from the start of the infusion by the trapezoidal rule. The fraction of carboplatin crossing the BBB was derived from the CSF AUC : plasma AUC ratios. Plasma carboplatin levels (c) vs time (t) data from the end of

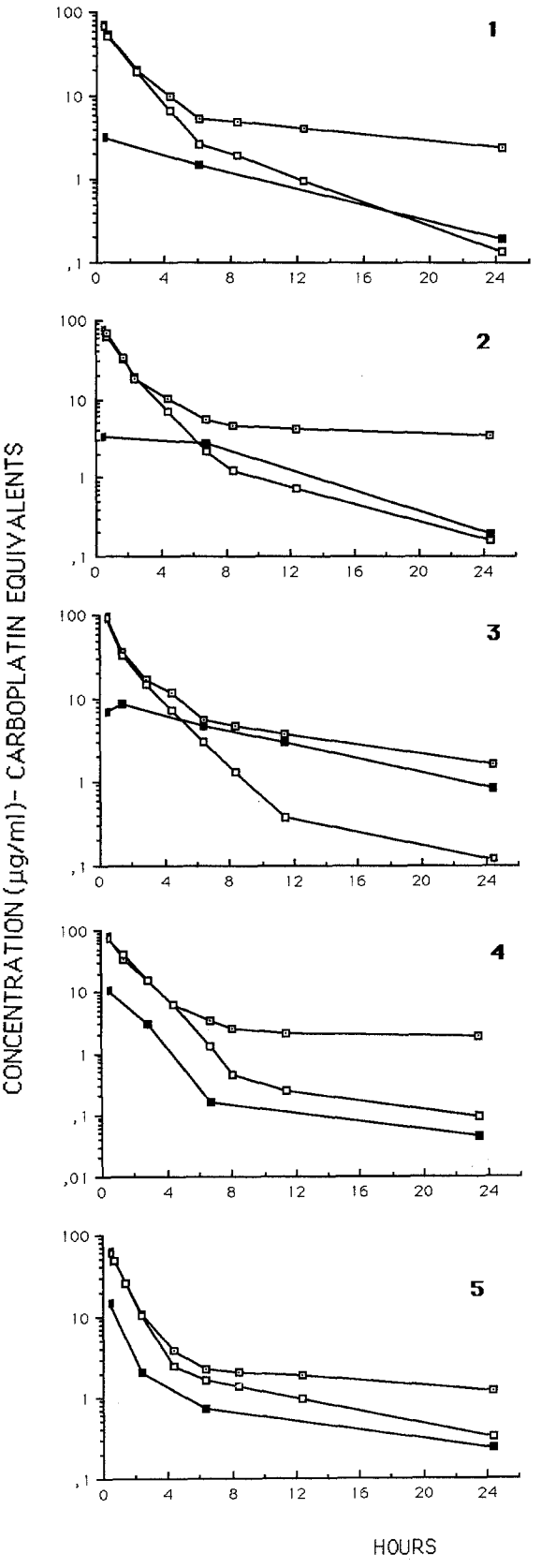

Fig. 1. Concentration vs time curves obtained for total plasma (⊡), UF plasma (□), and CSF (■) carboplatin following infusion of 600 mg/m^2 in 5 patients

Table 2. Pharmacokinetic parameters of UF carboplatin after a 1-h i. v. infusion of 600 mg/m^2

Patient	AUC (mg ml^{-1} min)		CSF/plasma	c_{EI}[a] (μg ml^{-1})		V_d (l)	Cl (l h^{-1})	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (h)
	CSF	Plasma		CSF	Plasma				
O. B.	1.56	9	0.17	2.8	56	7.33	3.78	61	4.3
I. W.	2.16	8.52	0.25	2.3	62	8.81	5.32	59	5.5
D. S. D.	4.38	9.48	0.46	5.8	78	6.02	3.24	72	7.7
L. R.	1.44	7.68	0.19	8.7	57	10.45	6.73	61	7.1
M. S.	1.92	6.24	0.31	12.7	55	3.87	3.37	32	6.5
Mean	2.29	8.18	0.28	6.5	62	7.30	4.49	57	6.21
± SD	1.20	1.27	0.12	4.3	10	2.53	1.50	15	1.34

[a] Concentration at the end of the infusion

the infusion to 24 h thereafter were fitted to a biexponential equation. The plasma pharmacokinetic parameters were calculated as follows, assuming an open two-compartment model [7]:

$$c = A \times e^{-\alpha \times t} + B \times e^{-\beta \times t},$$

Cl (systemic clearance) = dose/AUC,
K_{el} (elimination constant) = $\alpha \times \beta \times (A + B)/(A \times \beta + B \times \alpha)$,
V_d (apparent volume of distribution) = Cl/K_{el},
$t_{1/2\alpha}$ (first-phase half-life) = ln 2/α, and
$t_{1/2\beta}$ (second-phase half-life) = Pn2/β.

Results

Figure 1 shows the c vs t curves for free carboplatin in the plasma and CSF as well as the total platinum plasma levels expressed as carboplatin equivalents (i.e., platinum concentration $\times 1.91$) for the five patients studied. Table 2 shows the CSF and plasma pharmacokinetic parameters. The levels of free and total platinum in the CSF were similar, indicating that only a negligible fraction of the carboplatin was bound to proteins in the CSF. On the basis of the data points available, CSF carboplatin seemed to show a monoexponential pattern of decay in three subjects (patients 1–3) and a biexponential decay pattern in the two remaining patients.

Discussion

Although the BBB appears to be interrupted in many areas of brain tumors, a reduction in the transfer of hydrosoluble compounds from the brain capillaries to the tumor parenchyma has been demonstrated in a number of brain-tumor models [2]. The BBB appears to limit the drug concentration, especially near the proliferating edge of the tumor [11]. Therefore, the BBB is one of the factors limiting the efficacy of systemic chemotherapy in the treatment of brain tumors.

The CSF level of a solute present in the blood can be used as a measure of BBB permeability, since extracellular brain fluid is in equilibrium with the CSF. For optimal quantification of the amount of drug crossing the BBB, we used the ratio of CSF AUC : plasma AUC. In fact, simple consideration of the ratio of the CSF drug concentration and the corresponding plasma level, especially at later points, would have been erroneous, since most antineoplastic agents display slower kinetics in CSF.

CDDP, the first platinum compound used in clinical trials, is purported to cross the BBB in limited amounts; this observation is based on studies on CSF platinum levels performed in monkeys by Gormley et al. [9] and in humans by Stewart et al. [14]. In the latter study, platinum CSF concentrations were analyzed in eight patients with malignant brain tumors following the i.v. infusion of CDDP at doses ranging from 15 to 120 mg/m^2 on different schedules. Barely detectable or undetectable (0.1 μg/ml) levels of platinum were found in CSF sampled from 0 to 99 h after the end of the infusion. At autopsy, two patients with glioblastoma multiforme and one with intracerebral metastases of melanoma exhibited a high intratumor concentration of platinum [14]. This apparent contradiction was explained by the authors as being a consequence of the marked BBB disruption occurring in the vasculature of intracerebral tumor, whereas the intact BBB in other areas of the brain prevented the protein-bound CDDP from penetrating the CNS. Therefore, the platinum levels that accumulated in the tumor appeared to be adequate to exert the clinically observed antineoplastic activity. As compared with CDDP, a much smaller fraction of carboplatin binds to plasma proteins, essentially because the protein binding process of the latter is slower [15]. In a series of 20 patients treated in our division with 600 mg/m^2 carboplatin given as a 1-h infusion, only 23% of the delivered dose was protein-bound at 4 h after the end of the infusion [13].

In preclinical studies in mice, the administration of carboplatin produced levels of platinum in brain parenchyma that were higher than those obtained using CDDP at equitoxic doses [3]. Although the determination of the elimination half-life was not the main purpose of the present study, the half-lives calculated were similar to those previously reported by Newell et al. [12]. Given the limited sampling during the 1st h after the end of the infusion, we may have missed an early distribution phase in some of the patients studied. However, we observed a similar biexponential plasma decay in another six patients who were previously studied following additional sampling at 15, 30, and 45 min following the end of the infusion.

In our study, both plasma peak levels of carboplatin and AUC values showed limited interpatient variability. Carboplatin CSF levels showed substantial interpatient vari-

ability, with a >5-fold difference in peak levels and a 3-fold difference in AUC values being recorded. The interpatient difference in CSF pharmacokinetics may have been related at least in part to the different anatomical alterations induced by the surgical procedures or by the presence of a large tumor mass or to the secondary alterations in CSF dynamics, such as some degree of hydrocephalus or cerebral edema. The few data points available make it difficult to derive firm conclusions on the carboplatin elimination half-lives in the CSF. However, carboplatin seemed to show a monoexponential pattern of decay in three patients and a biexponential decay pattern in the other two subjects.

Carboplatin levels that have been reported to be cytocidal in vitro vary according to the different experimental systems used. In neuroblastoma cell lines, a 50% reduction in survival has been obtained following a 24-h exposure at doses ranging from 0.21 to 1.13 μg/ml; these values correspond to an AUC value varying from 0.3 to 1.58 mg ml^{-1} min [10]. Similar results were obtained in our laboratory using the human Med cell line TE-671; preliminary data show a 50% reduction in survival at mean doses of 1 ± 0.18 μg/ml following a 24-h exposure, corresponding to an AUC value of 1.44 ± 0.26 mg ml^{-1} min. The CSF carboplatin levels measured in all of our patients during the 1st day of the 2-day treatment were above the in vitro cytocidal levels. In three of the four patients who were evaluable for tumor response, we observed one complete remission and two partial remissions following two cycles of carboplatin infused at a dose of 1200 mg/m^2 that were repeated 1 month apart. No clear correlation between the degree of tumor response and either the CSF carboplatin levels or the CSF: plasma ratios could be observed. Obviously, the small number of patients studied limits the value of this pharmacodynamic analysis; however, both the clinical and the laboratory results of our study suggest that the dosage and the modality of administration of carboplatin used in our study were generally adequate. These observations may be helpful in establishing the optimal dose and schedule for carboplatin administration in the treatment of children with Med and other neuroectodermic CNS tumors.

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