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Difference in CDDP penetration into CSF between selective intraarterial chemotherapy in patients with malignant glioma and intravenous or intracarotid administration in patients with metastatic brain tumor

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Abstract Platinum (Pt) levels in plasma and cerebrospinal fluid (CSF) in patients with malignant glioma were determined after initiation of selective intraarterial chemotherapy with a combination of VP-16 (etoposide) and CDDP (cisplatin), and were compared with the CSF Pt levels in patients with metastatic brain tumors after intravenous or intracarotid administration of VP-16 and CDDP. CSF Pt levels were also compared for various administration routes, doses, CSF sampling routes and blood–CSF barriers in metastatic brain tumor. Changes in the blood-CSF barrier to CDDP during treatment in a patient with meningeal lymphoma and in a patient recovering from surgical removal of a metastatic brain tumor were also examined by periodic administration of CDDP. All CSF samples were taken through Ommaya reservoirs placed in the anterior horn of the lateral ventricle or the postoperative cavity. The mean peak CSF/plasma total Pt ratio (T/T ratio) and the mean CSF total Pt/plasma ultrafiltrable Pt ratio (T/U ratio) were highest (15.0% and 24.4%, respectively) following selective intraarterial infusion of CDDP in patients with malignant glioma, followed by intravenous infusion in meningeal carcinomatosis (11.5% and 18.9%), intracarotid administration (5.4% and 8.7%) and intravenous infusion (60 mg/m^2 2.5% and 100 mg/m^2 2.9%; and 60 mg/m^2 3.5% and 100 mg/m^2 7.7%) in patients with the solid type of metastatic brain tumor. In CSF obtained from the postoperative cavity in cases of metastatic brain tumor, T/T and T/U ratios were extremely high (40.9% and 62.4%). However, the CSF Pt level even after selective intraarterial administration of CDDP in malignant glioma was 0.51–1.64 μg/ml total Pt and 0.43–1.08 μg/ml ultrafiltrable Pt. Even the CSF level obtained from the postoperative cavity was 1.0–4.7 μg/ml total Pt. These low levels of total and ultrafiltrable Pt are considered not to be cytotoxic to disseminated cells in the CSF space and to normal brain cells. As for changes in the blood–CSF barrier, repeated administration of CDDP showed that the rate of entry of Pt into the CSF decreased in parallel with improvements apparent on CT scans in the patient with meningeal lymphoma, and also showed that the blood–CSF barrier to Pt was gradually repaired after the metastatic brain tumor had been removed.

Key words CDDP · Cerebrospinal fluid · Malignant brain tumor

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Introduction

The distribution of platinum (Pt) in the central nervous system in brain tissues, brain tumors and cerebrospinal fluid (CSF) has been reported [15, 21], and Pt in the CSF is not likely to have appreciable cytotoxicity, even when administered intravenously at the maximal dose, because of its low ratio of penetration into the CSF when the blood–brain barrier (BBB) remains intact. However, in cases in which the BBB is not completely intact or is modified to some extent, as occurs in patients with brain tumors [14, 23], higher concentrations of Pt are thought to be delivered into the extracellular space. Several studies on patients with malignant tumor and supposedly different grades of modified BBB have shown different ratios of Pt penetration into the CSF with different infusion intervals [1, 3, 4, 7]. In the present study, we evaluated the penetration of Pt into the CSF following selective intraarterial

infusion of CDDP (cisplatin) combined with infusion of VP-16 (etoposide) in seven patients with malignant glioma, and compared these results with those obtained from intravenous or intracarotid administration of CDDP in patients with intraparenchymal metastatic brain tumor and meningeal carcinomatosis from lung cancer.

Patients and methods

Patients

Selective intraarterial chemotherapy with a combination of VP-16 (60 mg/m^2) and CDDP (60 mg/m^2) was performed in five glioblastoma and two anaplastic astrocytoma patients by placing a microcatheter in the anterior cerebral artery (A1), middle cerebral artery (M1), posterior cerebral artery (P1/2) and basilar artery (basilar tip) and using 60-min pulse injections. The details of this therapy have been described elsewhere [17].

Intravenous drip administration of VP-16 and CDDP (60 or 100 mg/m^2 each) was performed in 30 patients with metastatic brain tumor (6 meningeal carcinomatosis, 24 intraparenchymal tumor). The nine patients in the group of POIV-100 and POIA-60 are included in the 24 patients with intraperenchymal metastatic brain tumor. In these patients, Osumaya reservoir was placed in both lateral ventricle and postoperative cavity and both pt levels were measured simultaneously. In four of the nine patients with metastatic brain tumors who received 100 mg/m^2 CDDP, the drug was administered intravenously, and five of the eight patients who received 60 mg/m^2 CDDP, the drug was administered via the carotid. Patients were divided into seven groups: the malignant glioma group receiving selective intraarterial infusion of 60 mg/m^2 CDDP (SIA-60, seven patients); the meningeal carcinomatosis group receiving intravenous injection of 60 mg/m^2 CDDP (MCIV-60, (six patients); the intraparenchymal metastatic brain tumor group receiving intravenous injection of 60 or 100 mg/m^2 CDDP (IV-60, eight patients; IV-100, nine patients); the intraparenchymal metastatic brain tumor receiving intracarotid injection of 60 mg/m^2 CDDP (IA-60, seven patients); and the intraparenchymal metastatic brain tumor group with Ommaya reservoirs placed in the postoperative cavity and receiving intravenous injection of 100 mg/m^2 CDDP and intracarotid injection of 60 mg/m^2 CDDP (POIV-100, four patients; POIA-60, five patients).

VP-16 was initially administered for 60 min followed by CDDP for 60 min. CDDP was administered to all patients in the afternoon to minimize the effect of circadian variations in Pt levels in the plasma and CSF between patients [11, 13].

Sampling and assay

In patients with malignant glioma, whole blood and CSF samples were collected at 10, 20, 40, 60, 80, 100, 120, 180 min, and 24 and 48 h after selective intraarterial infusion of CDDP was initiated. In patients with metastatic brain tumor, Ommaya reservoirs were also placed in the lateral ventricle and/or postoperative cavity. In this study, the postoperative cavity was defined as a closed area with no communication with the lateral ventricle, although it had communication with the subarachnoid space. Whole blood and CSF was then sampled at 0, 30, 60, 90, 120, 180 min, and 24 and 48 h after the 60-min intravenous or intracarotid injection was terminated. All timed whole blood and CSF samples were centrifuged for 10 min at 2300 rpm. Ultrafiltrable Pt was separated from plasma and CSF by centrifugal ultrafiltration for 15 min at 1000 g in an Amicon CF MPS-3 filter kit (Amicon, In: MA, USA). Pt in plasma, plasma ultrafiltrate, CSF and CSF ultrafiltrate were measured using an AA40 atomic absorption spectrometer (Varian Instruments, Ca, USA) set for 265.9 nm absorption. Pt in plasma and CSF before ultrafiltration was defined as total Pt (TP) and Pt in the ultrafiltrate was defined as ultrafiltrable platinum (UP). The lower limit of TP in the plasma was 50 ng/ml and that in the CSF and UP in the plasma and CSF was 25 ng/ml. VP-16 concentrations were quantified by high-performance liquid chromatography (HPLC Intelligent Autosampler: Japan Spectroscopic Co. Tokyo, Japan) equipped with a 290 nm absorption detector (Intelligent UV Spectrophotometric Detector, 875–UV). The detection limit was 0.1 μg/ml.

Pharmacokinetic analysis

From the concentrations of CDDP in the plasma and CSF, the pharmacokinetic parameters, C_{max}, AUC and $t_{1/2}$ were calculated from the start of injection by the trapezoidal rule using a non-compartmental moment method [24]. C_{max} was taken as the actual observed peak concentration. Least-squares linear regression analysis was used to ascertain the elimination rate constant (β) from the visually identified terminal linear portion of the log concentration vs time curve. The apparent elimination $t_{1/2}$was calculated as $t_{1/2} = \ln 2/\beta$. The area under the plasma and CSF concentration time curve (AUC) was calculated by the trapezoidal rule plus the quotient of plasma and CSF concentration at the last point assayed, divided by the elimination rate constant.

Results

Pt in the plasma and CSF following selective intraarterial infusion of VP-16 and CDDP in patients with malignant glioma (Fig. 1)

The concentration of VP-16 in the plasma reached its highest levels (8.0–13.2 μg/ml) upon completion of the 60-min infusion, but VP-16 was not detected in the CSF during or after infusion. Pt in the plasma showed peak concentrations (TP, 4.3–7.8 μg/ml; UP, 2.5–7.2 μg/ml) at the termination of intraarterial infusion of CDDP with a time-dependent increase in protein-bound Pt. Pt levels declined according to a biexponential model, with an initial half-life for TP of 40–60 min and terminal half-life of 24–80 h. At 24 h after termination of CDDP infusion, the mean TP level in the plasma was still high at 29.6% (1.0–2.8 μg/ml) of its mean peak concentration; UP was not detected in any of the patients. The levels of TP and UP in the plasma did not increase in any of the patients at the second intraarterial infusion 2 weeks later.

As for the penetration of Pt into the CSF, CSF concentrations reached measurable levels (54–260 ng/ml) at 10 min after infusion of CDDP had begun. TP reached peak concentrations (510–1635 ng/ml) at 0–120 min after termination of CDDP infusion and declined more gradually than the plasma concentrations. At 24 h after termination of CDDP infusion, TP was detected in all patients (mean $\pm$ SEM 332 ± 101 ng/ml, $n = 7$) at a mean level of 37.8% of the mean peak concentration. At 48 h, TP was still detected in all patients at a mean

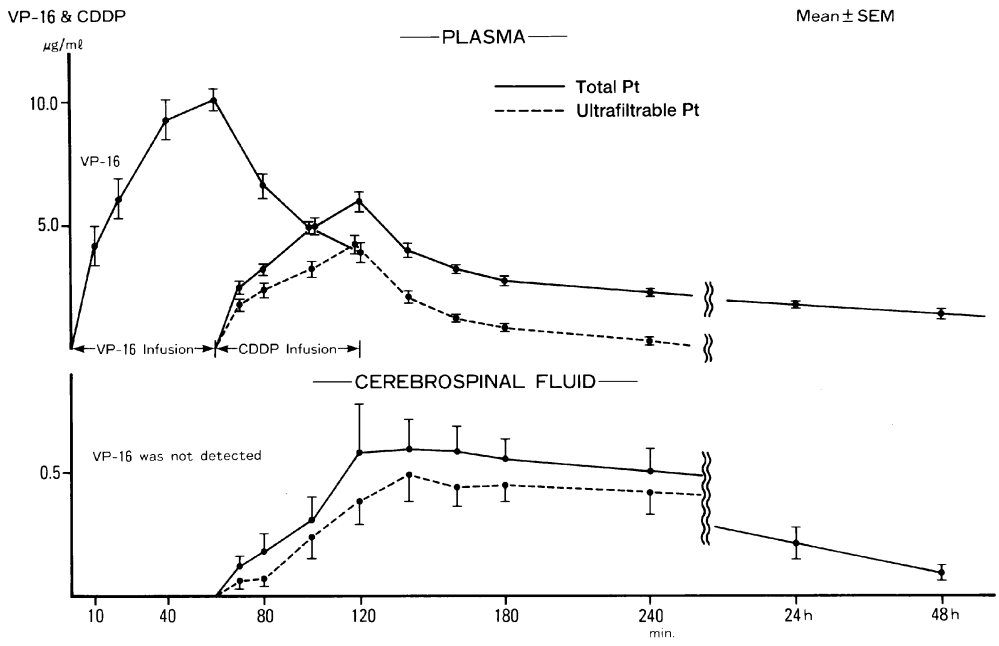

Fig. 1 Plasma and CSF concentrations of VP-16 and Pt in patients with malignant glioma after selective intraarterial infusion of 60 mg/m^2 VP-16 and 60 mg/m^2 CDDP using a microcatheter

level of 110 ng/ml. In contrast, UP was not detected in any of the patients at 24 h after termination of CDDP infusion.

Pt in plasma and CSF in patients with intraparenchymal metastatic brain tumors

Pt in plasma and CSF following intravenous injection of 60 or 100 mg/m^2 CDDP (Fig. 2)

Plasma concentrations of Pt were dose dependent, and the mean peak total concentration after the 100 mg/m^2 CDDP injection was 1.3 times higher than that after the 60 mg/m^2 CDDP injection. The concentration curve of Pt in plasma after the 60-min intravenous injection of CDDP showed the same levels and pattern as with selective intraarterial infusion of CDDP.

CSF peak TP concentration was also dose dependent. In the IV-60 group, the CSF peak TP level was less than 120 ng/ml in seven of the eight patients, and only one patient reached 393 ng/ml. In the IV-100 group, the CSF peak TP level was less than 220 ng/ml in eight of the nine patients, and only one patient reached 503 ng/ml.

In the two patients with multiple metastatic brain tumor, who had intravenous injections of 100 mg/m^2 CDDP three times weekly, Pt concentrations in the plasma and CSF were higher following each CDDP injection. However, this was not observed in the patients who had intravenous CDDP injections repeated at intervals of 2 months.

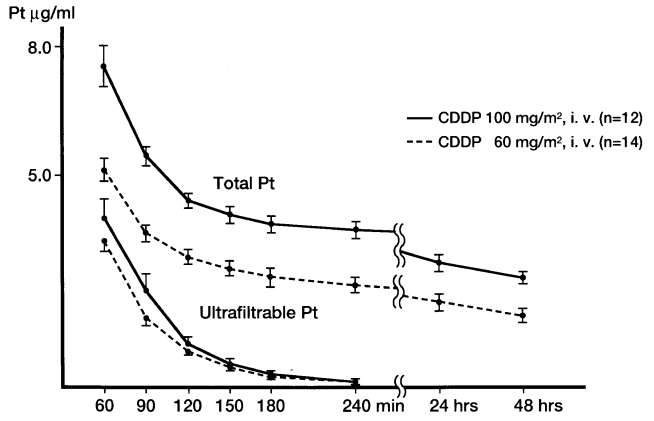

Fig. 2 Plasma concentrations of Pt in patients with brain metastasis after intravenous administration of 60 or 100 mg/m^2 CDDP

Pt in plasma and CSF following intracarotid injection of 60 mg/m^2 CDDP (Table 1)

Measurable levels of Pt in the CSF were observed in all patients, and peak TP ranged from 78 to 681 ng/ml. Mean peak TP in the CSF after the 60 mg/m^2 CDDP injection was approximately two times higher than that after the 60 mg/m^2 CDDP intravenous injection, although this difference was not significant (Table 2). However, in the three patients who had both intracarotid and intravenous CDDP injections, no differences in Pt concentrations in the CSF between those receiving intracarotid and intravenous injection were seen.

Table 1 Peak total platinum (Pt) in the CSF (*SIA-60* selective intraarterial chemotherapy with 60 mg of infusion, *MCIV-60*, meningeal carcinomatosis, *IV-100* intravenous injection of 100 mg/m^2, *IA-60* intrcarotid injection of 60 mg/m^2, *POIV-100* postoperative cavity, (intravenous injection of 100 mg/m^2, *POIA-60* postoperative cavity, intracarotid injection of 60 mg/m^2

Disease	Source of CSF[a]	Route of administration	Dose (mg/m^2)	Patient group	Peak total pt (ng/ml)	Mean ± SEM	*n*
Malignant glioma	Lateral ventricle	i.a.[b]	60	SIA-60	510–1635	886 ± 161	7
Meningeal carcinomatosis	Lateral ventricle	i.v.	60	MCIV-60	108–965	481 ± 121	6
Metastatic brain tumor (intraparenchymal)	Lateral ventricle	i.v.	60	IV-60	72–393	133 ± 38	8
		i.v.	100	IV-100	77–503	188 ±45	9
		i.a.[c]	60	IA-60	78–681	251 ±86	7
	Postopertive cavity	i.v.	100	POIV-100	1077–4710	2857 ± 807	4
		i.a.[c]	60	POIA-60	1013–3150	1885 ±406	5

[a]Location of Ommaya reservoir
[b]Selective intraarterial infusion
[c]Intracarotid infusion

Table 2 Statistical analysis (unpaired *t*-test) of CSF CDDP pharmacokinetic parameters determined under various conditions of CDDP infusion in malignant brain tumors (*T/T* ratio CSF/plasma total platinum ratio, *CSF/plasma AUC ratio* CSF/plasma total platinum AUC ratio, *NS* not significant, *A* selective intraarterial infusion (60 mg/m^2), *B* meingeal carcinomatosis (60 mg/m^2, i.v.), *c* intraparenchymal metastatic tumor (60 mg/m^2, i.v.), *D* intraparenchymal metastatic tumor (100 mg/m^2, i.v.), *E* intraparenchymal metastiatic tumor (60 mg/m^2, i.a.), *F* intraparenchymal metastatic tumor (100 mg/m^2, i.v., postoperative cavity), *G* intraparenchymal metastatic tumor (60 mg/m^2, i.a., postoperative cavity))

	CSF peak total Pt	T/T ratio	CSF/plasma AUC ratio	CSF total Pt AUC	CSF free Pt AUC	CSF total Pt $t_{1/2}$	CSF free Pt $t_{1/2}$
A–B	0.074 (NS)	0.539 (NS)	0.054 (NS)	0.022	0.058 (NS)	0.243 (NS)	0.040
A–C	0.004	0.007	0.012	0.004	0.034	0.000	0.020
A–D	0.006	0.007	0.013	0.005	0.035	0.004	0.024
A–E	0.005	0.023	0.014	0.005	0.037	0.000	0.022
A–F	0.096 (NS)	0.007	0.785 (NS)	0.058 (NS)	0.148 (NS)	0.320 (NS)	0.017
A–G	0.026	0.047	0.210 (NS)	0.154 (NS)	0.105 (NS)	0.231 (NS)	0.018
B–C	0.040	0.051	0.047	0.012	0.021	0.191 (NS)	0.084 (NS)
B–D	0.062 (NS)	0.063 (NS)	0.055 (NS)	0.006	0.026	0.215 (NS)	0.198 (NS)
B–E	0.139 (NS)	0.151 (NS)	0.063 (NS)	0.008	0.035	0.145 (NS)	0.124 (NS)
B–F	0.061 (NS)	0.006	0.010	0.028	0.030	0.300 (NS)	0.058 (NS)
B–G	0.030	0.026	0.016	0.022	0.181 (NS)	0.091 (NS)	0.047
C–D	0.631 (NS)	0.748 (NS)	0.768 (NS)	0.638 (NS)	0.666 (NS)	0.655 (NS)	0.560 (NS)
C–E	0.241 (NS)	0.242 (NS)	0.521 (NS)	0.683 (NS)	0.586 (NS)	0.562 (NS)	0.507 (NS)
C–F	0.042	0.016	0.016	0.016	0.023	0.273 (NS)	0.206 (NS)
C–G	0.014	0.014	0.010	0.010	0.039	0.030	0.187 (NS)
D–E	0.505 (NS)	0.281 (NS)	0.695 (NS)	0.932 (NS)	0.576 (NS)	0.585 (NS)	0.786 (NS)
D–F	0.044	0.016	0.017	0.017	0.024	0.278 (NS)	0.645 (NS)
D–G	0.015	0.015	0.010	0.011	0.043	0.030	0.251 (NS)
E–F	0.047	0.022	0.018	0.016	0.030	0.270 (NS)	0.128 (NS)
E–G	0.018	0.019	0.011	0.011	0.056 (NS)	0.026	0.100 (NS)
F–G	0.288 (NS)	0.716 (NS)	0.313 (NS)	0.581 (NS)	0.506 (NS)	0.363 (NS)	0.737 (NS)

Pt in CSF obtained through an Ommaya reservoir placed in the postoperative cavity (Fig. 3)

Much higher levels of CSF Pt were obtained following intravenous injection of 100 mg/m^2 and intracarotid injection of 60 mg/m^2 than through an Ommaya reservoir placed in the lateral ventricle ($P < 0.02$, Table 2). Maximum levels were from 1.0 to 4.7 μg/ml (mean ± SEM 2.32 ±0.43, $n = 9$). These levels were also much higher than those obtained from the lateral ventricle in patients with meningeal carcinomatosis.

Pt in plasma and CSF in patients with Meningeal carcinomatosis following 60 mg/m^2 CDDP injection (Figs. 2 and 3)

Peak CSF TP levels ranging from 108 to 956 ng/ml (mean ±SEM 481 ±121, $n = 6$) were obtained by intravenous injection of 60 mg/m^2. These values were higher than those obtained by intravenous or intracarotid administration of 60 or 100 mg/m^2 CDDP to patients with intraparenchymal metastatic brain tumor, although a significant difference was seen only between

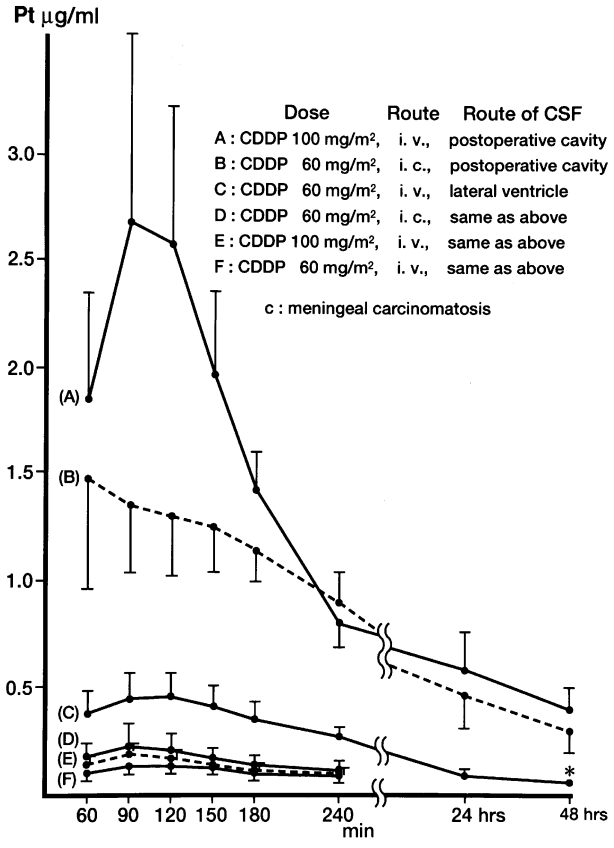

Fig. 3 CSF concentrations of Pt after intravenous (i.v.) or intracarotid (i.c.) administration in patients with intraparenchymal metastatic brain tumors or meningeal carcinomatosis. CSF was obtained through an Ommaya reservoir placed in the lateral ventricle or postoperative cavity. Group C comprised those patients with meningeal carcinomatosis (*asterisk* the concentrations of Pt were below the detection limit in three of six group C patients, and this point represents the average of six patients)

the MCIV-60 group and the IV-60 group. Moreover, Pt could be detected after 48 h in four of six patients, in contrast to the patients with intraparenchymal metastatic brain tumor, from whom all CSF samples were under the lower limit of detection at 48 h after CDDP infusion.

Change in blood-to-CSF barrier to Pt (Figs. 4 and 5)

The blood-to-CSF barrier to Pt was examined in a patient who had undergone surgical removal of a metastatic brain tumor located in the right basal ganglion, using periodical CDDP administrations and determining the Pt levels in the CSF obtained through an Ommaya reservoir placed in the postoperative cavity. CDDP 100 mg/m^2 was administered intravenously four times. The first administration was 1 week after surgery, the second 2 weeks after the first, the third 4.5 months after the second, and the fourth 5.0 months after the third. Extremely high levels of Pt were found following the first administration; the peak total CSF/plasma ratio was 50%. Penetration into the CSF was decreased following the second administration, with a peak total CSF/plasma ratio of 30%. The peak total CSF/plasma ratio was 8% following the third administration and 5% following the fourth administration. In this way, the blood-to-CSF barrier to Pt was repaired gradually after surgery.

In another patient with meningeal lymphoma, the blood to CSF barrier was determined using the CSF Pt levels obtained through an Ommaya reservoir placed in the lateral ventricle. VP-16 and CDDP both at a dose of 60 mg/m^2 were administered intravenously four times at intervals of 7 days. CSF Pt levels decreased in parallel with improvements apparent on CT scans, in tumor markers and in general CSF findings.

Peak CSF/plasma TP (T/T) ratio and peak CSF TP/plasma UP (T/U) ratio (Table 3)

Both ratios were highest in the SIA-60 group, followed in order by the MCIV-60, IA-60, IV-60 and IV-100 groups. In the intravenous injection group, two patients showed high T/T ratios (8.0% and 11.0%), but the T/T ratios never exceeded 4.0% (ranging from 1.1% to 3.1%) in the other 15 patients. On the other hand, the T/T and T/U ratios were extremely high in CSF obtained from the postoperative cavity.

AUC over 48 h and $t_{1/2}$ of Pt in plasma and CSF (Tables 2, 4)

The AUC (μg h/ml) of UP in the plasma was less than one-tenth that of TP. The plasma TP AUC was dose dependent and intravenous injection of 100 mg/m^2 produced values approximately 1.5 times higher than those for intravenous injection of 60 mg/m^2.

In the SIA-60 group, the AUC of TP in the CSF was one-fifth of that in the plasma and the AUC of UP was 80% of the AUC of TP. These values were 17 and 13 times higher for TP ($P < 0.005$) and 28 and 16 times higher for UP ($P < 0.05$) compared with those for the IV-60 and IA-60 groups. In the POIV-100 group, the AUCs of TP and UP were higher ($P < 0.02$ and 0.05) than those of the IV-100 group. The AUC of TP in the POIA-60 group was also significantly higher ($P < 0.02$) than that of the IA-60 group, although the difference between the AUCs of UP was not significant.

With regard to the half-life of Pt, $t_{1/2}$ (h) of UP in the plasma for both intraarterial and intravenous injection was approximately 1/100 that of TP. In CSF obtained

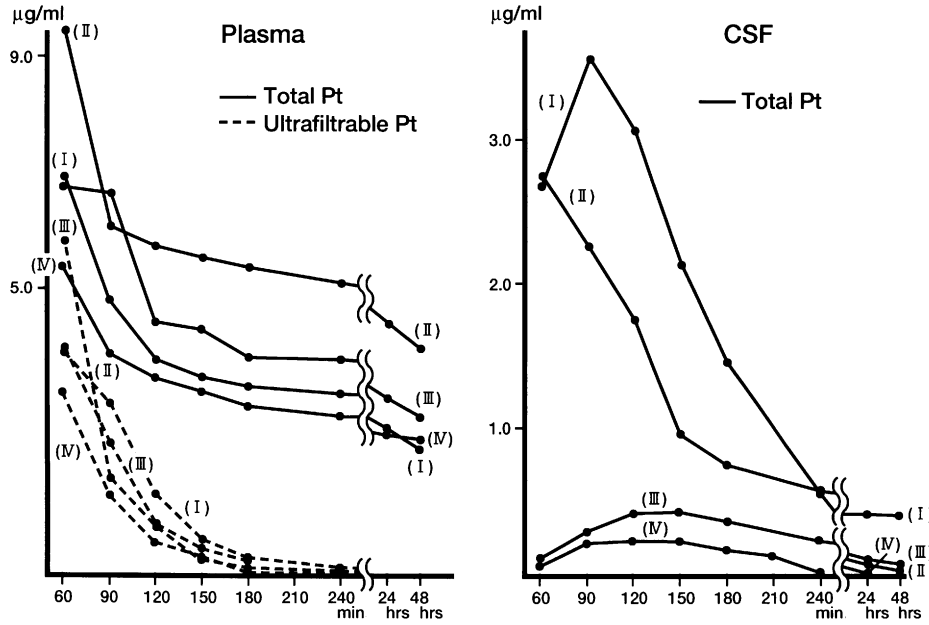

Fig. 4 Change in blood-to-CSF barrier to CDDP in a patient who had surgical removal of a metastatic brain tumor. CDDP (100 mg/m^2) was administered intravenously (*I–IV* first to fourth administration, respectively)

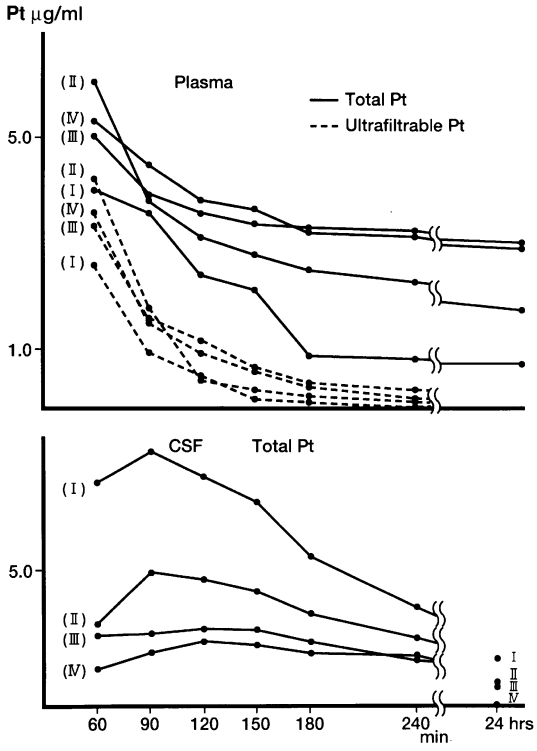

Fig. 5 Change in blood-to-CSF barrier to CDDP in a patient with meningeal lymphoma. VP-16 and CDDP at doses of 60 mg/m^2 were administered intravenously (*I–IV* first to fourth administration, respectively)

from the lateral ventricle, $t_{1/2}$ of TP was less than 22% of that of TP in the plasma, and the ratio of CSF TP to plasma TP ranged from 5% to 22% (mean $\pm$SEM 10.0 $\pm$3.2, $n=5$). In CSF obtained from the postoperative cavity, $t_{1/2}$ of TP was significantly longer ($P<0.05$) than in CSF obtained from lateral ventricle in the IA-60 group. However, in the POIV-100 group, there was no significant difference because of the small number of samples from the postoperative cavity subgroup. On the other hand, $t_{1/2}$ of UP in the CSF was longer than that of UP in the plasma. In particular, the $t_{1/2}$ of CSF UP in the SIA-60 group was longer than that in the MCIV-60, IV-60, IV-100, IA-60, POIV-100 and POIA-60 groups ($P<0.05$) and the CSF/plasma UP $t_{1/2}$ ratio in the SIA-60 group was extremely long (32.7 times) compared with that in the MCIV-60 (5.9 times), IV-60 (2.6 times), IV-100 (3.9 times), IA-60 (4.0 times), POIV-100 (1.9 times) and POIA-60 (2.1 times) groups.

CSF/plasma TP AUC ratio (Table 5)

When the levels of Pt were determined in CSF obtained from the lateral ventricle, the ratio was highest in the SIA-60 group, followed by the MCIV-60, IA-60, IV-60 and IV-100 groups. In CSF obtained from the postoperative cavity, the ratios were much higher than in CSF obtained from the lateral ventricle in the cases of metastatic brain tumor, including meningeal carcinomatosis, ranging from 14.1% to 59.0% with a mean of 31.3%.

Table 3 CSF/plasma peak total platinum (T/T) and CSF/plasma peak total/free platinum (T/F) ratios (for details of the patient groups, see Table 1)

Disease	Source of CSF[a]	Route of administration	Dose (mg/m^2)	Patient group	Ratio	Range of ratio (%)	Mean ± SEM	n
Malignant glioma	Lateral ventricle	i.a.[b]	60	SIA-60	T/T	6.6–30.3	15.0 ± 3.0	7
					T/F	7.1–61.2	24.4 ± 6.7	7
Meningeal carcinomatosis	Lateral ventricle	i.v.	60	MCIV-60	T/T	2.4–26.1	11.5 ± 3.4	6
					T/F	3.7–36.6	18.9 ± 5.5	6
Metastatic brain tumor (intraparenchymal)	Lateral ventricle	i.v.	60	IV-60	T/T	1.1–8.0	2.5 ± 0.8	8
					T/F	1.5–8.3	3.5 ± 0.8	8
		i.v.	100	IV-100	T/T	1.1–11.0	2.9 ± 1.0	9
					T/F	1.6–24.8	7.7 ± 2.8	9
		i.a.[c]	60	IA-60	T/T	1.0–16.8	5.4 ± 2.2	7
					T/F	1.8–28.4	8.7 ± 3.4	7
	Postoperative cavity	i.v.	100	POIV-100	T/T	18.3–65.4	40.9 ± 5.9	9
		i.a.[c]	60	POIA-60	T/F	28.4–92.7	62.4 ± 8.2	9

[a]Location of Ommaya reservoir
[b]Selective intraarterial infusion
[c]Intracarotid infusion

Table 4 Concentration-time AUC (μg h/ml) and half-life ($t_{1/2}$, h) of platinum in plasma and CSF (for details of the patient groups, see Table 1)

Disease	Source of CSF[a]	Route of administration	Dose (mg/m^2)	Patient group	Sample	Pt	AUC (0–48 h) (mean ± SEM, n)	$t_{1/2}$ (h) (mean ± SEM, n)
Malignant glioma	Lateral ventricle	i.a.[b]	60	SIA-60	Plasma	Total	85.7 ± 8.8, 7	85.0 ± 19.8. 7
						Free	5.7 ± 0.6, 7	0.6 ± 0.1, 7
					CSF	Total	17.6 ± 3.6, 7	18.6 ± 2.3, 7
						Free	14.0 ± 4.3, 7	19.1 ± 5.4, 7
Meningeal Carcinomatosis	Lateral ventricle	i.v.	60	MCIV-60	Plasma	Total	93.5 ± 16.5, 6	124.0 ± 35.8, 6
						Free	3.6 ± 0.4, 6	0.8 ± 0.1, 6
					CSF	Total	6.4 ± 1.4, 6	12.5 ± 4.6, 6
						Free	2.5 ± 0.6, 6	4.7 ± 1.2, 6
Metastatic brain tumor (intraparenchymal)	Lateral ventricle	i.v.	60	IV-60	Plasma	Total	106.5 ± 8.2, 8	75.6 ± 12.6, 8
						Free	5.2 ± 0.4, 8	0.8 ± 0.1, 8
					CSF	Total	1.0 ± 0.5, 8	4.4 ± 1.3, 8
						Free	0.5 ± 0.2, 8	2.1 ± 0.2, 8
			100	IV-100	Plasma	Total	154.7 ± 7.9, 9	81.0 + 8.1, 9
						Free	4.9 ± 0.8, 9	0.7 ± 0.8, 9
					CSF	Total	1.5 ± 0.8, 9	5.8 ± 2.7, 9
						Free	0.7 ± 0.2, 9	2.7 ± 0.9, 9
		i.a.[c]	60	IA-60	Plasma	Total	104.8 ± 10.2, 7	66.2 ± 7.4, 7
						Free	4.6 ± 0.9, 7	0.6 ± 0.1, 7
					CSF	Total	1.4 ± 0.8, 7	3.3 ± 1.1, 7
						Free	0.9 ± 0.4, 7	2.4 ± 0.4, 7
	postoperative cavity	i.a.[c]	60	POIA-60	Plasma	Total	77.9 ± 5.4, 5	66.7 ± 14.7, 5
						Free	3.7 ± 0.3, 5	0.7 ± 0.1, 5
					CSF	Total	27.2 ± 5.5, 5	29.7 ± 7.5, 5
						Free	4.5 ± 1.3, 5	1.5 ± 0.3, 5
		i.v.	100	POIV-100	Plasma	Total	125.4 ± 2.7, 4	70.9 ± 5.2, 4
						Free	6.1 ± 1.2, 4	0.7 ± 0.1, 4
					CSF	Total	32.1 ± 6.5, 4	133.3 ± 96.3, 4
						Free	5.8 ± 1.2, 4	1.3 ± 0.7, 4

[a]Location of Ommaya reservoir
[b]Selective intraarterial infusion
[c]Intracarotid infusion

Table 5 AUC (0–48 h) CSF/plasma total platinum ratio (%)

	Patient group	Location of Ommaya reservoir	AUC CSF/plasma Total pt (mean ± SEM, *n*)
Selective intraarterial infusion in malignant glioma	SIA-60	Lateral ventricle	23.04 ± 6.19, 7
Intravenous injection in meningeal carcinomatosis	MCIV-60	Lateral ventricle	7.98 ± 2.68, 6
Intravenous injection in intraparenchymal metastasis		Lateral ventricle	1.01 ± 0.39, 16
60 mg/m^2	IV-60		0.87 ± 0.39, 7
100 mg/m^2	IV-100		1.12 ± 0.65, 9
Intracarotid injection in intraparenchymal metastasis	IA-60	Lateral ventricle	1.56 ± 0.93, 7
Intravenous injection in intraparenchymal metastasis	POIV-100	Postoperative cavity	25.56 ± 5.17, 4
Intracarotid injection in intraparenchymal metastasis	POIV-60	Postoperative cavity	35.82 ± 7.29, 5

Discussion

CDDP binds not only to proteins but also to low molecular weight nucleophiles. The result is the formation of three kinetically distinct forms of Pt: parent drug, protein-bound Pt and Pt bound to low molecular weight compounds. The last of these has been referred to as mobile metabolite. It is filtrable but is nevertheless a metabolite and presumably a theoretically inactive form of Pt [6, 12]. However, owing to technical difficulties, attempts to quantify free CDDP directly have seldom been made. To our knowledge, the only report of free CDDP quantification involved the estimation of free CDDP using a physiological model [6, 12]. The most commonly used measure of cytotoxic platinum-related material in plasma is UP. Consequently, UP Pt, measured in the present study, is a mixture of parent drug and mobile metabolite.

The normal BBB restricts the entry of most water-soluble compounds into brain tissue [18]. However, the blood vessels of brain tumors are structurally altered and the BBB is partially disrupted [14, 23], making the BBB and the permeability–surface area product of the tumor capillaries limiting factors to drug delivery to brain tumors and brain adjacent to the invading tumor. It is clear that non-protein-bound CDDP is more easily transported across the BBB than protein-bound CDDP. Non-protein-bound CDDP has been reported to be the active component of CDDP [2, 8, 22] and is rapidly eliminated or metabolized to an inactive complex. Therefore, selective intraarterial administration of CDDP by placing the tip of a microcatheter at the main supplying arteries is considered a better means of delivering non-protein-bound CDDP to the tumor area than intravenous or intracarotid administration because of the lower drug dilution, due to lower blood flow in the smaller artery, and the higher percentage and dose of non-protein-bound CDDP administered. It seems resonable to suppose that Pt levels in the ultrafiltrate are very close to the level of free Pt for at least a short period of time after administration of CDDP.

One of the advantages of this therapy over the more usual intracarotid injection may be the effect of the intraarterial infusion of VP-16 which modifies the BBB [20]. Indeed, the analysis of CDDP penetration into the CSF obtained from the lateral ventricle in malignant brain tumors using three different administration routes (intravenous, intracarotid and selective intraarterial) indicated that the degree of CDDP penetration was highest in the SIA-60 group. Considering that CDDP toxicity is dependent on the concentration and duration of exposure [5, 19], and that non-protein-bound CDDP is the active component, we may expect this therapy to potentially prevent dissemination of glioma cells. Indeed, a patient with glioblastoma and meningeal dissemination who was treated with selective intraarterial chemotherapy with VP-16 and CDDP showed improvements in the CSF general findings (cell counts) after chemotherapy (unpublished data).

However, following the suggestions that Pt is mainly in the form of parent drug for the first 10 min and is mostly a fixed metabolite after only 2 h following administration [6, 12] and that the cytotoxicity of Pt in the CSF may depend on whether it is in the form of parent drug or mobile metabolite, the UP in the CSF may be mostly in the form of mobile metabolite and therefore therapeutically inactive. If this theory is true, it is questionable whether these findings on the CSF distribution show a benefit of selective intraarterial chemotherapy. We have to wait for the development of a new assay for free Pt before a conclusion can be drawn.

As for the differences in CDDP penetration into the CSF between intravenous and intracarotid infusion for metastatic brain tumor, there were no significant differences in blood-to-CSF transport of Pt between the two infusion routes, although a larger dose of CDDP was delivered to the tumor area by intracarotid infusion. Therefore, intracarotid infusion should not be used to increase blood-to-CSF transport of Pt in order to kill the disseminated tumor cells.

As for changes in the blood–CSF barrier, the penetration of CDDP into the CSF was increased in meningeal carcinomatosis even by intravenous injection. The local blood–CSF barrier was also disrupted by surgery and the disruption was much greater in the postoperative cavity than in meningeal carcinomatosis. However, the blood–CSF barrier was restored by effective chemotherapy in meningeal carcinomatosis and naturally in the postoperative cavity. CSF Pt levels in the SIA-60 and MCIV-60 groups probably had appreciable cytotoxicity. The Pt levels were very high in CSF obtained from the postoperative cavity in nine patients. These levels (1.0–4.7 μg/ml) are considered to be locally cytotoxic. Thus, postoperative CDDP therapy might prevent local tumor recurrence, especially following metastatic brain tumor, because the postoperative tumor cavity in these cases is a relatively closed area and these tumor cells are sensitive to CDDP. The time to local recurrence after tumor removal has been shown to be longer in patients receiving CDDP chemotherapy than in those receiving chemotherapy with other anticancer agents [16].

As for penetration of CDDP into the CSF, experimental and clinical data in various disease conditions have been reported. Experimental data from rhesus monkeys has shown that the CSF/plasma ratio at the time of the peak CSF value following an intravenous bolus injection is 2–3% and never exceeds 4%, and that the CSF Pt concentration falls below the limit of detection within 2.5 h of injection [9]. Although the ratio of peak CSF to peak plasma was not determined in that study, this value following an intravenous bolus injection is considered to be almost equal to or less than the value (peak CSF/plasma TP ratio 1.1–11.0%, mean 2.7%, in CSF from the lateral ventricle) following a 60-min injection in metastatic brain tumor patients in the present study, considering that the peak CSF Pt levels following a 60-min intravenous injection were less than those following the intravenous bolus infusion.

In clinical research, DeGregorio et al. found CSF concentrations 2.9% of the plasma TP and 43.5% of the plasma UP 2 h after the end of a 2-h infusion of 120 mg/m^2 CDDP in a patient with neuroblastoma who had prior surgical resection of the tumor followed by full craniospinal radiation therapy [3]. In a patient with relapsed glioblastoma after radiation and chemotherapy, the peak CSF/plasma TP ratio (calculated from the graph presented; the exact value was not given) was approximately 1.4% [1]. The values presented in these two reports were almost equal to those of the solid metastatic brain tumor group in the present study. In contrast, DeGregorio et al. found high Pt penetration into the CSF (peak CSF/plasma TP, 7.0–9.6%, as calculated from the graph presented) in a 3-year-old boy with recurrent ependymoma who was initially treated with surgery and radiation therapy [4].

Ginsberg et al. reported the results of pharmacokinetic studies of bleomycin, CDDP and vinblastine in the CNS of a patient with a primary germ-cell tumor of the brain who had received 90 Gy of prior radiotherapy. Significant concentrations of bleomycin and cisplatin were produced in the CSF following intravenous administration (peak CSF/plasma TP ratio ranged from 11% to 33%, as calculated from the graph presented) [7]. These values are high and almost equal to those in the patients with malignant glioma treated with selective intraarterial VP-16/CDDP chemotherapy. However, in both these reported studies, the patients had recurrent or relapsed tumors, and the BBB may have been modified by irradiation [10] to a much greater degree than the cases of newly diagnosed malignant glioma in the present study. These cases are therefore not comparable with the cases in the present study.

In this way, the blood-to-CSF barrier to CDDP is altered according to the stage of the brain tumor or the presence of adjuvant therapy such as chemotherapy or radiotherapy. When the barrier is disrupted to a large extent, as occurs in meningeal carcinomatosis or surgical manipulation, CDDP penetrates into the CSF easily following intravenous injection. However, in cases of newly diagnosed malignant glioma and intraparenchymal metastatic brain tumor, the blood-to-CSF barrier is maintained to a greater degree than in meningeal carcinomatosis, and the administration route becomes important, especially in malignant glioma.

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