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A Phase I Study of Intracarotid Artery Infusion of *cis*-Diamminedichloroplatinum(II) in Patients with Recurrent Malignant Intracerebral Tumors[1]

David J. Stewart,[2] Sidney Wallace, Lynn Feun, Milam Leavens, Sue Ellen Young, Stanley Handel, Giora Mavligit, and Robert S. Benjamin

Departments of Developmental Therapeutics [D. J. S., R. S. B., L. F., G. M.], Diagnostic Radiology [S. W., S. H.], and Surgery [M. L., S. E. Y.], The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030

ABSTRACT

A Phase I study of intracarotid *cis*-diamminedichloroplatinum was performed in 11 patients with intracerebral tumors (five glioblastoma, four melanoma, one meningeal sarcoma, and one lung carcinoma) progressing after radiation ± chemotherapy. The internal carotid artery was temporarily cannulated by a percutaneous transfemoral approach. All patients received i.v. heparin, mannitol, and fluids; seven received dexamethasone, 50 mg i.v., twice the day before and the day of treatment. Intracarotid *cis*-diamminedichloroplatinum, 60 to 100 mg/sq m in 175 to 250 ml 0.45% NaCl solution with 1000 units heparin, was infused over 1 hr. Six patients received two or more courses (maximum of 6) at 2- to 8-week intervals. Gastrointestinal toxicity was mild to moderate. Ototoxicity was minor. Central nervous system (CNS) toxicity was focal, severe, permanent, and possibly due to embolus in one patient at 75 mg/sq m; focal and reversible in one patient at 100 mg/sq m; and generalized but reversible in one patient at 75 mg/sq m. Possible CNS toxicity was noted in two additional patients. Two patients with CNS toxicity developed permanent ipsilateral retinal toxicity, and one patient without CNS toxicity developed bilateral decreased visual and auditory acuity 2 weeks after his sixth treatment. Renal and hematological toxicity and orbital pain were mild. Response status included: early death, one; probable responses, six (2+, 4+, 6, 6+, 8, and 8+ months); stabilization, two (3+ and 4 months); and failure, two. We recommend *cis*-diamminedichloroplatinum (60 mg/sq m) every 2 to 4 weeks for Phase II studies. Severe CNS and retinal toxicity are possible.

INTRODUCTION

Both glioblastoma multiforme and brain metastases from extracerebral primaries continue to have a very bad prognosis (1, 6, 13). While palliation may be obtained using nitrosoureas in malignant glioma (5), long-term survival is extremely rare (2) as is response of brain metastases to systemic chemotherapy. Over the past several years, i.c. infusion of various antineoplastic agents has been attempted, and response rates appear to have been augmented for at least some drugs using this approach (3). Drugs that have been studied include methotrexate, 5-fluorouracil, cyclophosphamide, triethylenethiophosphoramide, vincristine, vinblastine, and nitrogen mustard (3). A recent study of i.c. bischloroethylnitrosourea reported substantial activity against intracerebral metastases from carcinoma of the lung (14).

Recent studies from M. D. Anderson Hospital have demonstrated that DDP[3] is both tolerable and effective when administered i.a. in the treatment of regionally confined cancers (4). In addition, we have demonstrated that local peak concentration and area under the concentration × time curve of platinum are augmented by administering DDP i.a. (11) and that platinum attains high concentrations in intracerebral tumor after i.v. DDP (12). Moreover, both primary brain tumors (8, 9) and brain metastases (10) have responded to i.v. DDP. In an attempt to enhance the response rate of intracerebral tumors to this drug, we performed a Phase I study of i.c. artery infusion of DDP.

MATERIALS AND METHODS

Eleven patients with intracerebral neoplasms recurrent after cranial irradiation and systemic chemotherapy were entered into this study. All patients gave voluntary consent after being fully informed of the investigational nature of this study and of the potential for very severe neurological or ophthalmological complications. Diagnoses were glioblastoma multiforme (5 patients), malignant melanoma (4 patients), meningeal sarcoma (one patient), and small-cell undifferentiated carcinoma of the lung (one patient). All patients were symptomatic from their tumor and had a life expectancy of ≤2 months. Pretreatment Zubrod performance status was Level 1 in one patient, Level 2 in 6 patients, Level 3 in 2 patients, and Level 4 in 2 patients. Median age was 48 years (range, 23 to 58 years).

Prior to DDP infusion, patients received 1 liter of fluids i.v. over 2 hr and mannitol, 10 g i.v., over 15 min. The internal carotid artery was cannulated using a transfemoral fluoroscopy-guided approach. Heparin, 3000 units, was given i.v. at the initiation of the catheterization and each hr the catheter was in place to decrease the possibility of embolic complications. A pump was used to administer DDP (60 to 100 mg/sq m in 175 to 250 ml 0.45% NaCl solution) with 1000 units heparin into the carotid artery over 1 to 1.5 hr. Mannitol, 40 g, was given i.v. over 2 hr. Treatments were repeated at 2- to 8-week intervals. Seven of the patients received parenteral dexamethasone, 50 mg, twice a day the day before and the day of treatment. All patients were also receiving stable maintenance doses of dexamethasone. Selected patients had ophthalmological evaluations before and after treatment, and others had electroencephalographic monitoring before and during treatment. Vital signs were assessed periodically during the treatment. Complete blood counts and differential and platelet counts were obtained weekly, and serum blood urea nitrogen and creatinine were measured prior to each treatment. Response status was determined on the basis of clinical neurological examination and CT of the brain. Complete re-

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[2] To whom requests for reprints should be addressed, at Ontario Cancer Foundation Clinic, Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario, Canada K1G 8L6.

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[3] The abbreviations used are: i.c., intracarotid; DDP, *cis*-diamminedichloroplatinum; i.a., intraarterially; CT, computerized axial tomography.

sponse was defined as complete normalization of the neurological examination and CT. Probable response was defined as unequivocal improvement in either one or both of the neurological examination or CT that could not be explained on the basis of change in steroid doses alone. Stable disease was defined as no major change in neurological examination or CT. Progressive disease was defined as unequivocal worsening of either the neurological examination or CT.

Postmortem examinations were obtained on one patient who died 6 days after her first i.c. treatment and one patient who died 3 months after his third i.c. treatment.

RESULTS

Toxicity is outlined in Table 1. Three patients received only one course of treatment, 4 patients received 2 courses, 2 patients received 3 courses, one patient received 5 courses, and one patient received 6 courses.

Gastrointestinal toxicity was dose related and was generally mild to moderate. Renal toxicity was also very mild. Bone marrow toxicity was seen only with DDP (100 mg/sq m) and consisted of reversible thrombocytopenia. Auditory toxicity was seen in 3 patients. One patient (Patient 8) who received 3 treatments developed ipsilateral tinnitus and a complaint of hyperacusis. A second patient (Patient 3) was noted to have ipsilateral subclinical loss of high frequency tones on an audiogram performed 2 days after his first treatment. Transient ipsilateral orbital pain developed in 2 patients.

The most serious toxicities were neurological and retinal. Definite retinal toxicity developed in 2 of the 11 patients, and possible retinal toxicity developed in a third patient. In the first patient (Patient 1), mild blurring of vision in the ipsilateral eye was noted after his first treatment at a dose of DDP (60 mg/sq m) and worsened after subsequent courses at 100 mg/sq m. The second patient (Patient 5) developed permanent ipsilateral blindness after her first treatment of DDP (75 mg/sq m). Electroretinography confirmed that the visual impairment was due to retinal damage. Patient 11 developed bilateral decreased visual and auditory acuity 2 weeks after his sixth treatment that may possibly have been due to treatment.

Both patients with definite retinal toxicity also developed neurological toxicity. Patient 1 had no neurological sequelae from his first treatment at a dose of DDP of 60 mg/sq m, but 24 hr after his second treatment at a dose of 100 mg/sq m, he developed headache, lethargy, focal seizures, and contralateral motor weakness. A CT examination of the brain revealed edema of the entire ipsilateral cerebral hemisphere. After 7 days of treatment with mannitol and dexamethasone, the neurological symptoms and cerebral edema resolved, and the patient was discharged. He subsequently tolerated a third treatment at a dose of DDP of 60 mg/sq m with no problem. Patient 5 developed moderate nausea and vomiting 3 hr after her first and only treatment, during which she received a dose of DDP of 75 mg/sq m infused into the left carotid artery. Following the first episode of vomiting, she developed transient blurring of vision in the left eye, and immediately following the second episode of vomiting, she developed the abrupt onset of left-sided blindness, aphasia, and a dense right hemiparesis. Subsequent CT examinations revealed evidence of a cerebral infarct, suggesting an embolic etiology. Gradually, incomplete recovery occurred over the next 4 months. A third patient (Patient 8) developed mild generalized weakness approximately 1 week after his third treatment of DDP at a dose of 75 mg/sq m. Serum biochemistry, including magnesium, was normal. Further treatment was withheld, and he gradually improved. A fourth patient (Patient 3) experienced a single focal seizure that could possibly have been treatment related 24 hr after his second treatment at a dose of DDP of 60 mg/sq m.

A fifth patient (Patient 10) who was deteriorating rapidly with dysphasia, decreased level of consciousness, and right hemiparesis at the time he received DDP (90 mg/sq m) continued to deteriorate after treatment at about the same rate over a period of 1 week, stabilized in this condition for several weeks, and then gradually improved to a level comparable to his pretreatment level. It was not clear to what extent his posttreatment deterioration represented toxicity, but it was assumed that it was more a result of the natural history of his disease.

Electroencephalography monitoring during treatment in 4 patients revealed no acute changes.

Of the 11 patients, one patient was classified as a tumor-related early death. She died 1 week after treatment and at autopsy had no pathological changes that could be attributed to the treatment. Of the 10 evaluable patients, 6 were probable responders including 2 patients with malignant melanoma (2+ and 4+ months), 2 patients with glioblastoma multiforme (8 and 8+ months), one patient with small-cell undifferentiated carcinoma of the lung (6+ months), and one patient with meningeal sarcoma (6 months) (Table 2). All 6 responders had both CT scan and neurological evidence of response, although the CT scan changes were quite minor in 2 of the patients. No patient had complete disappearance of tumor on CT scan, although Patient 1 died of his systemic disease 6 months after initiation of treatment and at autopsy had no residual viable intracerebral tumor, although presence of intracerebral tumor had been proven surgically previously. No pathological evidence of vasculitis or neuronal damage was found at autopsy, although it was this patient who had developed ipsilateral cerebral edema after receiving DDP (100 mg/sq m).

Two additional patients developed disease stabilization. This included one patient with glioblastoma multiforme (4 months)

Table 1
Toxicity of i.c. DDP

DDP (mg/sq m)	Total no. of courses	No. of courses with toxicity						
		Central nervous system	Retinal[a]	Auditory[a]	Nausea, vomiting	Renal	Orbital pain	Myelosuppression
60	21	1[b]	3	2	2	1		
75	7	2	1	2	7	1	2	
90	1	1[b]			1			
100	1	1	1					1

[a] Total of 3 patients affected; may not have been treatment related in one.
[b] May not have been treatment related.

Table 2
Summary of effects of DDP treatment regimen

Patient	Tumor type	Dose of DDP (mg/sq m)	No. of courses	Retinal toxicity[a]	Central nervous system toxicity[b]	Response status (mos.)
1	Oat cell	60–100	3	Yes	Yes	Response[c] (6+)
2	Melanoma	60	2	No	No	Response[c] (2+)
3	Melanoma	60	2	No	Possible	Failure
4	Melanoma	60	2	No	No	Response (4+)
5	Melanoma	75	1	Yes	Yes	Stable (3+)
6	Glioblastoma	60	2	No	No	Failure
7	Glioblastoma	60	5	No	No	Response (8+)
8	Glioblastoma	75	3	No	Yes	Response (8)
9	Glioblastoma	75	1	No	No	Early death
10	Glioblastoma	90	1	No	Possible	Stable (4)
11	Meningeal sarcoma	60	6	Possible	No	Response (6)

[a] Irreversible in all 3 patients.
[b] Reversible in 4 of 5 patients.
[c] Died of extracerebral tumor, while central nervous system disease was still responding.

and one patient with malignant melanoma (3+ months). Two patients failed to respond to treatment and died shortly after their second course of i.c. DDP. The patient with glioblastoma who progressed on treatment was the only patient on the study who had received DDP i.v. previously.

DISCUSSION

New agents or methods are greatly needed for the treatment of intracerebral neoplasms (13). While long-term survivors have been reported after treatment of brain metastases (7) and malignant gliomas (2), these are rare. Median survival duration with brain metastases is only approximately 4 months (1, 6), and with glioblastoma multiforme, it is only 11 to 12 months with optimal treatment (13). By 24 months from diagnosis, less than 20% of glioblastoma patients generally remain alive (13).

Our Phase I study of the i.c. infusion of DDP indicates that this treatment modality is capable of producing tumor regression or stabilization in patients whose tumor was progressing following initial treatment with cranial irradiation and systemic chemotherapy. It should be stressed, however, that response status of intracerebral tumors may be quite difficult to evaluate, and far larger numbers of patients will have to be studied before any meaningful conclusions can be drawn regarding its true therapeutic potential. In addition, very severe neurological and retinal toxicity may result, although the only patient developing permanent neurological toxicity probably suffered an embolic event rather than drug-mediated toxicity.

We currently recommend a dose of DDP of 60 mg/sq m for Phase II i.c. infusion studies. Of the 7 patients evaluable for response at this dose, 5 responded, while of 21 evaluable courses, the only serious toxicity was unilateral retinal toxicity in one patient, although Patient 11 experienced what may have been retinal toxicity after 6 courses. It was possible to repeat this dose every 2 to 4 weeks. Long-term follow-up will be necessary to assess whether delayed neurological or retinal toxicity will occur, and we do not currently recommend this as front-line treatment.

It is possible that prolonging the duration of the infusion might decrease the potential for retinal and neurological complications by decreasing the peak DDP concentration. However, this would also increase the chance of embolic complications. Moreover, the role of heparin in the etiology of the retinal and neurological complications is unclear, and by making infusions more rapid, it would be possible to omit the heparin. In addition, hydration may not be necessary with the dose of DDP used and could augment cerebral edema as could the use of 0.45% NaCl solution as the diluent for the DDP. The last 7 patients treated on this Phase I study received high doses of dexamethasone shortly before and after their i.c. infusion in an attempt to decrease neurological complications. This did not appear to be of major benefit, as 3 of the 5 patients with possible neurological toxicity and 2 of 3 with retinal toxicity were treated in this manner.

In summary, i.c. infusion of DDP may be effective against intracerebral tumors but may also result in severe neurological or ophthalmological toxicity and is not advocated as front-line treatment. We recommend a dose of DDP of 60 mg/sq m repeated every 2 to 4 weeks for Phase II studies.

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