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Phase I clinical trial of ormaplatin (tetraplatin, NSC 363812)

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Ormaplatin is a platinum analog that was developed because of an altered toxicity profile and non-cross resistance to cisplatin in both *in vitro* and *in vivo* models. To determine the toxicities and maximum tolerated dose of ormaplatin on a daily times five schedule, patients with refractory solid tumors received ormaplatin on five consecutive days at nine dose levels ranging from 1.0 to 15.0 mg/m^2/day. A total of 35 patients received 70 cycles of therapy. Nausea and vomiting and myelosuppression were moderate and not dose-limiting. Dose-limiting neurotoxicity, consisting of a sensory peripheral neuropathy, was seen in all five patients who received cumulative doses greater than or equal to 165 mg/m^2. This neurotoxicity was symptomatic in all patients and caused significant functional impairment in four patients with inability to walk in two patients. A sensitive atomic absorption spectroscopy analysis performed for one patient at the 13.0 mg/m^2/day dose level showed a Cp_{max} of 163 ng/ml and a $t_{1/2}$ of 10.9 min for free platinum. A phase II dose could not be determined due to the onset of peripheral neuropathy at low cumulative doses and not at absolute dose levels.

Key words: Neurotoxicity, ormaplatin, phase I trial.

Introduction

Cisplatin is one of the most active anticancer agents available and is widely used in the treatment of a variety of patients' tumors. Ormaplatin is one of many second generation platinum analogs synthesized and evaluated in the search for a platinum complex with comparable or superior antitumor activity and reduced toxicity.[1] Ormaplatin (Figure 1) is a diaminocyclohexane (DACH) platinum (IV) complex which is transformed spontaneously *in vivo* to a platinum (II) compound like cisplatin.[2] It is the platinum (II) complex that is the active moiety.

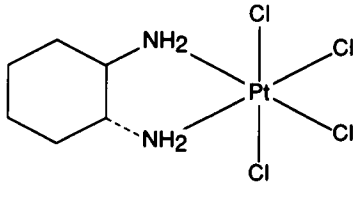
Compared with cisplatin, ormaplatin demonstrates similar or superior cytotoxic activity in cisplatin-sensitive cell lines *in vitro* and *in vivo*.[1,3–5] Also, cisplatin-resistant cell lines may retain sensitivity to ormaplatin or demonstrate incomplete cross-resistance.[4–10] In animal toxicology studies, ormaplatin was less nephrotoxic than cisplatin[11,12] and other toxicities seemed to be less. Based on these possible advantages the phase I trial described below was undertaken.

Materials and methods

Patient eligibility

Eligibility criteria were standard for a phase I study. Patients must have had a solid tumor with a microscopically confirmed diagnosis of metastatic disease. They were required to (i) have failed known forms of effective therapy as well as other investigational agents of higher potential efficacy,

ORMAPLATIN



NSC 363812 Tetraplatin

Tetrachloro(d,1–trans)1,2–diaminocyclohexaneplatinum (IV)

Figure 1. Structure of ormaplatin.

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(ii) have a performance status of 2 or better (Southwest Oncology Group criteria), (iii) have a life expectancy of 12 weeks and (iv) have recovered from the toxic effects of prior treatment. Adequate organ function was also required, manifest by: marrow function by WBC $\geq 3000/mm^3$, granulocytes $\geq 1500/mm^3$, platelets $\geq 100\,000/mm^3$ and hemoglobin ≥ 10 gm/dl; liver function by bilirubin ≤ 1.5 mg/dl, AST $\leq$ twice normal, and normal PT and PTT; renal function by creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 ml/min, and an inactive urinary sediment; metabolic function by electrolytes within 10% of normal and glucose ≤ 200 mg/dl; audiogram with no worse than moderate, symmetric, high frequency hearing loss; and no history of peptic ulcer disease, symptomatic peripheral neuropathy or congestive heart failure. Prior treatment with cisplatin was allowed. Women of childbearing potential were required to have a negative pregnancy test. Written informed consent was obtained according to federal and institutional guidelines.

Treatment plan

Each cycle consisted of ormaplatin administered once daily for five consecutive days with cycles repeated every 28 days. The drug was provided by the Division of Cancer Treatment of the National Cancer Institute as a yellow lyophilized powder in sterile 50 mg vials. The contents of each vial were reconstituted in 10 ml of sterile water, with each 1 ml containing 5 mg of ormaplatin, 9 mg of sodium chloride and 50 mg of mannitol, and then diluted in 250 ml of normal saline for administration intravenously over 30 min.

The first treatment cycle was given on an inpatient basis. Subsequent cycles could be given as an outpatient. Hydration fluids, consisting of a minimum of D5/0.5 Normal Saline administered at 100 ml/h, 4 h before and after treatment, were given to inpatients. Subsequent outpatient cycles were given with the same hydrating fluid at 150 ml/h for 2 h before and 3 h after treatment. After nausea and vomiting were seen at the first two dose levels, prophylactic antiemetics were administered with a combination of metoclopramide (2 mg/kg) and diphenhydramine (50 mg) given intravenously 1 h before ormaplatin. Intravenous dexamethasone (20 mg) and lorazepam (1 mg) were added to this prophylaxis, as well as post-treatment doses of metoclopramide, 1 and 3 h after ormaplatin, if they were necessary.

In mice, the LD_{10} was 10.44 mg/m^2/day on a daily times five schedule.[13] The initial dose level was 0.1 $MELD_{10}$ or 1 mg/m^2/day. A minimum of three evaluable patients were entered at each dose level with additional patients treated at a dose level if significant toxicity was seen. Dose levels were 1.0, 2.0, 3.3, 5.0, 7.0, 9.0, 11.0, 13.0 and 15.0 mg/m^2/day. Patients were removed from study if life-threatening toxicity (grade 4 hematologic, grade 3 non-hematologic) was observed or if disease progression occurred.

Prior to treatment patients were evaluated with a complete history and physical, complete blood count, chemistry panel, magnesium, amylase, PT and PTT, urinalysis, electrocardiogram, chest X-ray, audiogram, 24 h urine for protein and creatinine, and scans necessary for tumor measurement. Patients were seen weekly during treatment with performance of a history and physical examination as well as laboratory studies to include a complete blood count, chemistry panel, magnesium, amylase, PT and PTT, and urinalysis. Toxicity was graded using the common toxicity criteria and response was evaluated with standard criteria.

Table 1. Patient characteristics

	No. of patients
Patient demographics	
total	35
male	16
female	19
median age (range)	58 (35–75) years
Performance status	
0	7
1	22
2	6
Prior therapy	
none	4
radiation therapy	5
chemotherapy	7
both	19
Primary tumor sites	
lung	
non-small cell	9
small cell	1
colorectal	7
breast	6
prostate	2
melanoma	2
uterine sarcoma	2
kidney	2
gastric	1
parotid	1
fallopian tube	1
renal pelvis (transitional cell)	1

Pharmacokinetics

Pharmacokinetic samples of blood and urine were collected on at least two patients at each dose level during the first treatment cycle. Samples were to be analyzed using an HPLC assay as described by Andrews *et al.*[14] One patient's plasma samples were analyzed for free platinum using atomic absorption spectroscopy of an ultrafiltrate of plasma using the technique of Goel *et al.*[15]

Results

Thirty-five patients were entered on this study, receiving 70 cycles of treatment. Patient characteristics are summarized in Table 1. There were 16 males and 19 females, with a median age of 58, and good performance status, with the majority having a performance status of 1. The most common tumor types in patients treated were non-small cell lung, colon and breast cancer. The trial was concluded without a phase II dose determined when dose-limiting neurotoxicity occurred at relatively low cumulative doses of drug.

Neurotoxicity was the dose-limiting toxicity and was related to cumulative dose rather than dose level. The first patient to exhibit neurotoxicity was a 67 year old white male with squamous cell carcinoma of the lung, recurrent 6 months after local

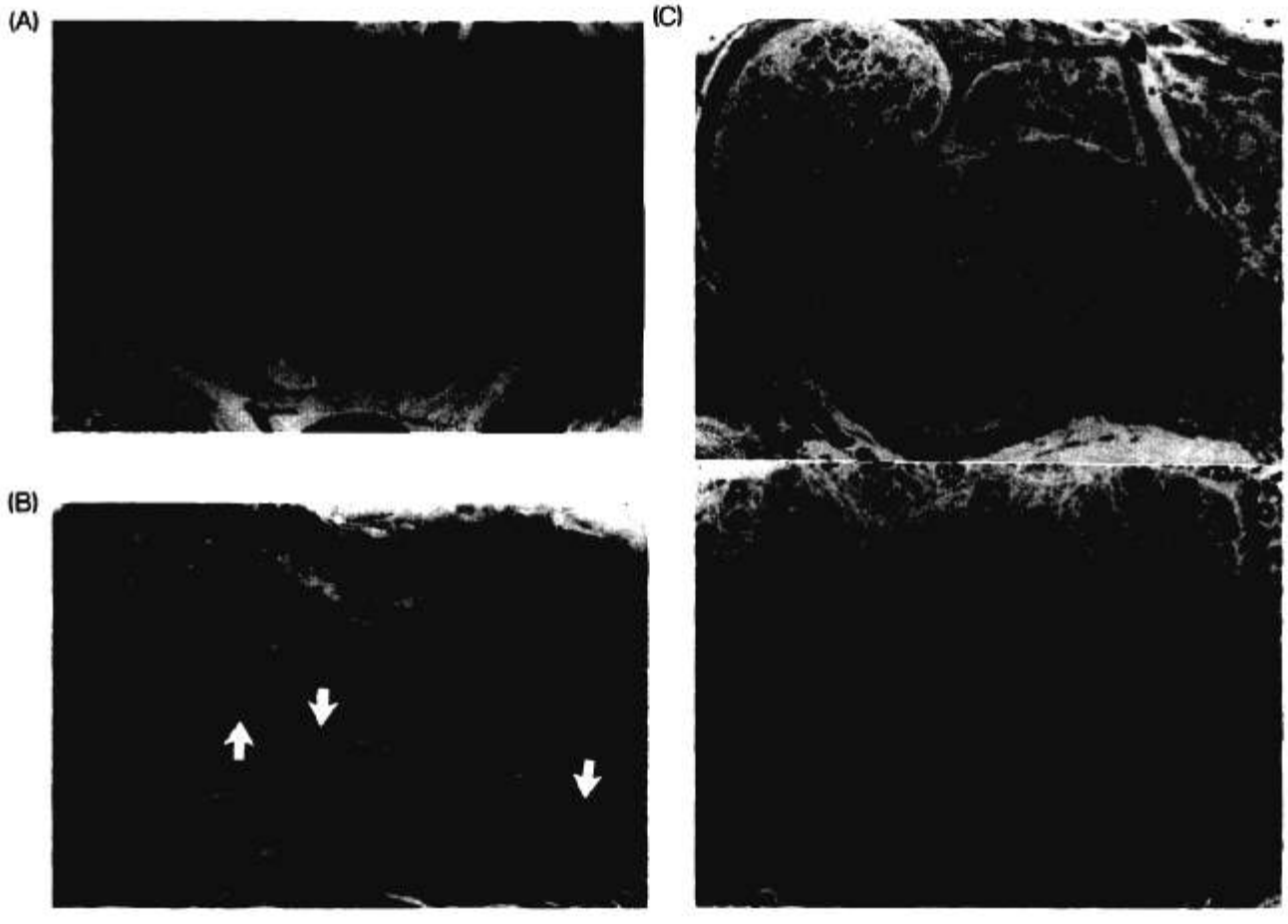

Figure 2. Sural nerve biopsy on patient 13. (A) Normal sural nerve. (B) Photomicrographs of myelinated nerve fibers reveal reduction in large myelinated axons and early remyelination. (C) Luxol fast blue (myelin)/H & E stain of longitudinal section of sural nerve reveals reduction in myelin sheath.

radiation therapy to a dose of 60 gray. He presented during the fifth cycle of treatment at the 7 mg/m^2/day level with numbness and paresthesias of the distal extremities. Two weeks after the completion of treatment, reflexes were decreased in the upper extremities and absent in the lower. Position and vibration sense were decreased in the fingers and toes. Motor, cerebellar and mental status tests were normal. Nerve conduction studies were compatible with a peripheral sensory neuropathy, showing prolonged peak latencies and decreased amplitudes on the sensory exam in both upper extremities and absent sural nerve signals. Motor conduction was normal. Other diagnostic studies, including B_{12} and folate levels, ANA, SPEP, lumbar puncture and head CT scan, were normal. Over the next month the neuropathy progressed to a severe gait difficulty, requiring a wheelchair. A sural nerve biopsy showed mild axonal loss with secondary demyelination and remyelination (Figure 2). Incomplete recovery was observed over the next 6–12 months, but the patient recovered to the point that he could walk with a walker.

Additional cases of neuropathy were subsequently observed and are summarized in Table 2. The neuropathy was consistently a sensory neuropathy and was only seen after repeated cycles of treat-

Table 2. Neurotoxicity of ormaplatin

Patient no.	Dosage level (mg/m^2/day)	No. of cycles	Cumulative dosage (mg/m^2)	Toxicity grade	Prior potential neurotoxins	Comment
13	7.0	5	175	3	none	A 67 year old male with squamous cell carcinoma of the lung noticed paresthesias after the fifth cycle of treatment that progressed to a severe gait disturbance. Exam and nerve conduction studies were abnormal, showing a sensory neuropathy. Sural nerve biopsy showed axonal loss, demyelination and remyelination. Patient was confined to a wheelchair.
20	11.0	3	165	3	etoposide	A 63 year old female with non-small cell lung cancer whose initial symptoms were during her third cycle with severe extremity pain and impairment of all sensory modalities. She was unable to cross-stitch or turn the pages of a book. Nerve conduction studies were abnormal. Prior treatment included chest radiation therapy and oral cyclophosphamide/ etoposide. Three months after her last treatment there was moderate improvement in paresthesias with amitryptiline therapy.
21	11.0	4	220	2	none	A 72 year old male with prostatic carcinoma who complained of moderate numbness in fingers and toes 3 months after the last dose, which was present for several more months. Evaluation showed mildly decreased vibration sense and nerve conduction studies which were abnormal.
24	11.0	4	220	3	none	A 60 year old male with renal cell carcinoma noticed numbness and tingling 1 month after the last dose which gradually increased. He later complained of difficulty writing and walking. Exam showed a severe sensory neuropathy with decreased proprioception, vibration and deep tendon reflexes in the lower extremities. Neurometer study showed no response at any frequency.
28	13.0	4	260	3	none	A 65 year old male with adenocarcinoma of lung who noticed numbness of fingers 1 week into his fourth cycle. Two months after his last treatment he was unable to button clothes or use door keys. On exam there was decreased vibratory and light touch sensation. EMG was normal but nerve conduction was compatible with sensory neuropathy in both upper and lower extremities.

Table 3. Nausea and vomiting noted with administration of ormaplatin

Dosage level (mg/m^2/day)	No. of patients at level	Cycles with toxicity grade				
		0	1	2	3	4
1.0	3	1	1	2	0	0
2.0	3	3	0	0	1	0
3.3	3	4	0	1	0	0
5.0	3	5	2	3	0	0
7.0	3	4	6	0	0	0
9.0	3	2	2	0	0	0
11.0	6	5	6	3	0	0
13.0	7	7	5	0	0	0
15.0	4	3	1	3	0	0

ment. The onset of symptoms was often delayed and only partially reversible.

Nausea and vomiting was seen at the first two dose levels, and the occurrence of this toxicity is summarized in Table 3. After the observance of this symptom at the first two dose levels, prophylactic antiemetics were administered for new patients and for subsequent treatments with a metoclopramide based combination. After this point nausea and vomiting was modest (of grade 1–2 severity) and was readily manageable, but occurred in most patients.

Diarrhea (of grade 1–2 severity) was noted in 17 of 35 patients and 21 of 70 treatment cycles, but was felt to be related to the antiemetic regimen which contained metoclopramide.

There was no evidence of ototoxicity with serial audiograms. Neither was renal toxicity seen, although this may have been obscured by the policy of administering hydration fluids to all patients throughout the trial.

Hematologic toxicity is summarized in Table 4 and, as can be seen, was sporadic at the higher dose levels but was not dose limiting. The toxicity reported is actually less than would appear since those patients with grade 3 myelosuppression each had other factors, such as bone marrow involvement, extensive prior treatment or intercurrent disease, that contributed to their cytopenias. As shown in Table 5, the nadir from myelosuppression tended to occur late in each cycle and sometimes delayed subsequent treatments.

The pharmacokinetic analysis was hampered by the fact that peak concentrations of the drug achieved, at the dose levels tested, were near the limits of the sensitivity of the HPLC assay. Pharmacokinetic data is thus limited to a single patient at the 13 mg/m^2/day dose level whose samples from day 5 were analyzed by atomic absorption spectroscopy for free platinum levels. This analysis yielded a Cp_{max} of 163 ng/ml and a $t_{1/2}$ of 10.9 min.

No evidence of antitumor activity, as determined by minor, partial or complete responses of measurable tumors, was observed in the patients enrolled on this trial.

Discussion

Neurotoxicity is a recognized complication of treatment with cisplatin. When observed, a peripheral neuropathy is the dose-limiting neurotoxicity and is described as a distal, symmetric, sensory neuropathy, predominantly affecting large nerve fibers and similar to the polyneuropathy of B_{12} deficiency. Initial symptoms are numbness or paresthesias. Deep tendon reflexes are decreased and there is loss of vibratory and position sense. This may progress to a severe sensory ataxia. These symptoms may develop and progress after cisplatin has been stopped and may not resolve.[16] Toxicity is dose-

Table 4. Hematologic toxicity of ormaplatin

Dosage level (mg/m^2/day)	No. of patients at level	No. of cycles with given grade of toxicity																			
		anemia					leucopenia					neutropenia					thrombocytopenia				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1.0	3	2	1	1	0	0	4	0	0	0	0	3	1	0	0	0	4	0	0	0	0
2.0	3	2	2	0	0	0	2	2	0	0	0	4	0	0	0	0	4	0	0	0	0
3.3	3	1	2	2	0	0	4	1	0	0	0	5	0	0	0	0	5	0	0	0	0
5.0	3	1	7	2	0	0	6	4	0	0	0	10	0	0	0	0	6	4	0	0	0
7.0	3	7	2	1	0	0	7	1	2	0	0	9	1	0	0	0	8	1	1	0	0
9.0	3	0	2	1	1	0	3	0	0	1	0	3	0	1	0	0	3	0	1	0	0
11.0	6	4	1	7	2	0	8	3	2	1	0	9	4	1	0	0	7	3	2	1	0
13.0	7	6	3	2	0	1	9	3	0	0	0	11	0	1	0	0	9	2	0	1	0
15.0	4	4	3	0	0	0	4	2	1	0	0	3	2	1	1	0	4	1	2	0	0

Table 5. Time pattern of myelosuppression in patients with toxicity

	Nadir count (#/mm^3)[a] median (range)	Nadir day[a] median (range)
Leucopenia	3170 (1900–3900)	18 (4–38)
Neutropenia	1587 (854–1960)	23 (7–52)
Thrombocytopenia	86000 (29000–137 000)	27 (10–39)

[a] Only for cycles with at least grade 1 toxicity.

related and cumulative, with patients usually receiving total doses of 300–600 mg/m^2.[17,18] Other neurotoxicities, noted with cisplatin, were not observed in our trial, including ototoxicity, autonomic neuropathy, retinopathy, cranial neuropathy and encephalopathy.[16]

In the present study, the neurotoxicity seen was related to the cumulative dose and not the absolute dose level given. All five patients who received a cumulative dose of 165 mg/m^2 or greater experienced peripheral neurotoxicity and in four of the five this toxicity was grade 3. On the other hand, the remaining 30 patients all received cumulative doses of less than 165 mg/m^2 and did not experience neurotoxicity as graphically depicted in Figure 3. Given the severity of this untoward reaction, the delayed onset of symptoms and their incomplete reversibility, the study was closed with no phase II dose recommended.

Five other phase I trials of ormaplatin on both the same and different schedules have been reported in preliminary form.[19–23] Four of these studies report neurotoxicity. In a phase I trial of intraperitoneal ormaplatin, one patient had grade 4 neuropathy at a cumulative dose of 331.5 mg/m^2. Three patients receiving total doses from 155 to 211 mg/m^2 had no neurotoxicity.[19] In the NCI trial of an every 28 days schedule, one patient developed grade 2 sensory peripheral neuropathy after a cumulative dose of 255 mg/m^2 over five cycles of treatment.[20] In the Wisconsin trial of the same every 28 days schedule, one of four patients receiving cumulative doses greater than 120 mg/m^2 developed neuropathy.[21] In a phase I trial of a day 1 and day 8 schedule, three patients developed a sensory polyneuropathy. This was related to cumulative dose of ormaplatin and patients receiving total doses greater than 200 mg/m^2 were at greater risk.[23] Thus, most other trials have shown neurotoxicity, although most instances have occurred in our daily times five schedule.

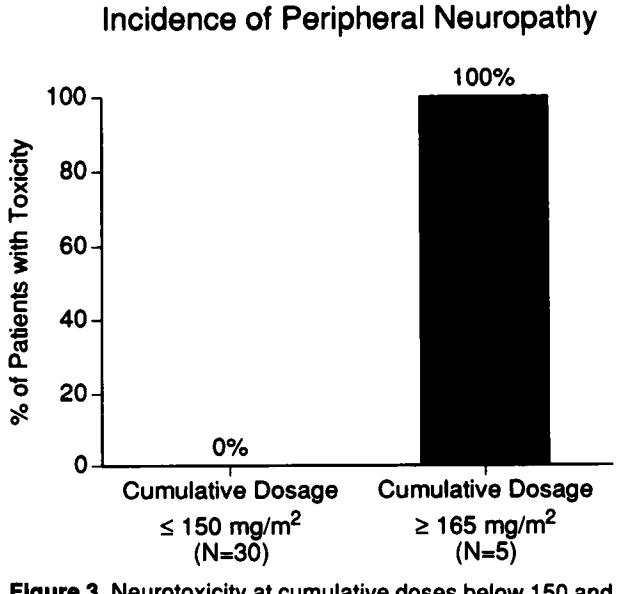

Figure 3. Neurotoxicity at cumulative doses below 150 and above 165 mg/m^2.

Approaches that might avoid this toxicity include the use of neuroprotective agents. Two of these agents, WR2721 or Org 2766, have been reported to have some benefit in clinical trials with patients receiving cisplatin.[24,25] Other possibly useful agents include glutathione, which has entered clinical trials,[26] and nerve growth factor, which has shown a protective effect in a rat model of cisplatin neuropathy.[27] Different schedules of drug administration or the use of specific stereoisomers of ormaplatin might also have less toxicity. However, given the results of our trial, further development of ormaplatin as a single agent on this schedule cannot be recommended, without some method to ameliorate the significant neurotoxicity observed.

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