Cancer Chemother Pharmacol (1997) 40: 439–443

CLINICAL TRIAL REPORT

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Zeniplatin in advanced malignant melanoma and renal cancer: phase II studies with unexpected nephrotoxicity

Received: 16 March 1996 / Accepted: 25 March 1997

Abstract The antitumor activity of zeniplatin, a third-generation, water-soluble platinum compound that has shown broad preclinical antitumor activity and no significant nephrotoxicity in phase I trials, was tested in patients with advanced malignant melanoma and advanced renal cancer. Patients who had not previously been treated, except with local limb perfusion and immunotherapy, were given zeniplatin as bolus injections at 125 mg/m^2 every 3 weeks. The main hematological toxicity was leukopenia (7/30 patients, WHO grade ≥ 3) and the main nonhematological toxicity was nausea and vomiting (21/30 patients, WHO grade ≥ 2). Serious nephrotoxicity was observed early in the renal cancer study and, later, also in the melanoma study. Hyperhydration did not prevent the nephrotoxicity, and the studies were stopped after 6 renal cancer patients and 24 malignant melanoma patients had been included. Zeniplatin gave objective responses in 3 of the 21 evaluable malignant melanoma patients [2 complete responses (CRs) in patients with lymph-node metastases lasted 5 and 14 months, respectively; 1 partial response (PR) in a patient with lymph-node and liver metastases lasted 6 months]. In the renal cancer study, only four patients were evaluable for response and none responded. The results show that zeniplatin has some activity (14%) in patients with advanced malignant melanoma, but no conclusion can be drawn regarding the activity of zeniplatin in renal cancer as the number of patients was too low. The main toxicities were leukopenia and nausea and vomiting. Unexpected and serious nephrotoxicity was observed, and for this reason the studies were terminated before the planned number of patients had been included. A possible explanation for the nephrotoxicity may be drug interactions, but no firm conclusion can yet be drawn.

Key words Zeniplatin · Malignant melanoma · Renal cancer · Nephrotoxicity

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Introduction

Zeniplatin, [2,2-bis(aminomethyl)-1,3-propanediol-*N*,*N*′] (1,1-cyclobutane-dicarboxylato) (2-)-*O*,*O*′ platinum, is a third-generation, water-soluble platinum compound. In animal tumor models and human tumor xenograft studies, zeniplatin showed a spectrum of antitumor activity different from that of cisplatin and carboplatin [3, 5]. In the murine tumors B-16 malignant melanoma and M5076 reticulum-cell sarcoma, zeniplatin was more active than cisplatin and carboplatin, and in the H207 human ovarian carcinoma it had comparable antitumor activity. Zeniplatin also had a therapeutic index 8-fold better than that of cisplatin and 2-fold better than that of carboplatin.

In the phase I clinical evaluation of zeniplatin given at doses ranging from 8.0 to 145 mg/m^2 by i.v. bolus administration, leukopenia was the dose-limiting toxicity [4]. Abnormal creatinine clearance values were obtained at different zeniplatin dose levels, but there was

no significant change in serum levels of creatinine or blood urea nitrogen (BUN). One patient with malignant melanoma and one patient with renal cancer showed an objective tumor response in the phase I trial.

Zeniplatin has previously shown activity in advanced non-small-cell lung cancer [6], metastatic breast cancer [8], and ovarian carcinoma [9]. It has also demonstrated some activity in a pilot study in advanced malignant melanoma [7]. For further investigation of the antitumor activity of zeniplatin in advanced malignant melanoma and in patients with advanced renal cancer, two phase II studies were initiated.

Patients and methods

Eligibility criteria included informed consent; histological or cytological documentation of malignant melanoma or renal cancer; and locally advanced, non-resectable, or metastatic disease with measurable, progressive lesions. Patients with brain or leptomeningeal metastasis, second malignancies, other serious illness, or allergy to cisplatin or carboplatin were not accepted for inclusion. Other eligibility criteria were an age of >18 years, a life expectancy of >3 months, a performance status (WHO) of ≥2, a WBC count of >4,000/μl, a platelet count of >100,000/μl, a serum bilirubin level of <26 μmol/l, and a serum creatinine value of <140 μmol/l. If the creatinine value was between 90 and 140 μmol/l, creatinine clearance was measured and the required value for study inclusion was >60 ml/min. The hepatic enzymes (SGOT, SGPT, and alkaline phosphatase) had to be within twice the limit of normal.

Prior chemotherapy, except for adjuvant regional chemotherapy with extracorporeal circulation for malignant melanoma patients with a treatment-free interval of less than 6 months, was not allowed. Prior immunotherapy with interferon and or interleukin II was accepted. A minimum of 4 weeks must have elapsed since surgery and radiotherapy before the entry into the protocol. The indicator lesion may not have been irradiated, but new lesions within a previously irradiated field were acceptable.

Standard WHO criteria were used for assessment of toxicity and response. Medical history, physical examination, and blood chemistries were repeated before every cycle. Complete blood cell counts were repeated once a week. The tumor parameters were assessed by physical examination every 3 weeks and by computerized tomography (CT) scan and ultrasound every 6 weeks. The patients were accrued during the period ranging from November 1989 until February 1991.

Drug administration

Zeniplatin was given i.v. over 90 min every 3 weeks at a dose of 145 mg/m^2. The drug was supplied by the American Cyanamid Company as lyophilized powder in 25- or 50-mg amber vials. Each vial was reconstituted with sterile water to yield a final concentration of 2.5 mg/ml. The drug was then transferred to an infusion bag containing 250 ml of 5% dextrose in water using one 0.22-μm Millimex-65 filter for each vial to avoid precipitation. The solution was light-sensitive and the infusion bag was covered with aluminium foil during the infusion. No hyperhydration was prescribed.

Dose modification

In patients with WHO grade IV leukopenia of <1,000 WBC/μl, or grade IV thrombocytopenia of <25 000 platelets/μl, at scheduled retreatment the zeniplatin dose was reduced by 25% in the subsequent treatment cycle. If the nadir WBC value was >4,000/μl or the platelet nadir was >100 000/μl the drug dose was increased by 20%. In the event of late bone marrow recovery the treatment interval was delayed by up to 2 weeks.

Antiemetic treatment

Initially antiemetics were given as needed during the first cycle and if unacceptable nausea and vomiting occurred. Prophylactic antiemetic therapy was given during the subsequent cycles. As the study progressed, nausea and vomiting were noted to be major subjective side effects. This required prophylactic administration of antiemetics to all patients, even during their first chemotherapy cycle.

Response evaluation

Patients were evaluable for response after they had completed two cycles of treatment. Patients with progressive disease at the end of second cycle were removed from the study and treated with alternative regimens. The treatment was continued in patients showing partial (PRs) or complete responses (CRs) until disease progression or the occurrence of excessive toxicity. In patients with stable disease the treatment was discontinued after three cycles. The duration of a PR was calculated from the start of therapy until documentation of progression, whereas the duration of a CR was calculated from the date the CR was established until disease progression.

Results

Table 1 summarizes the characteristics of the 24 patients with malignant melanoma and the 6 patients with renal cancer. Among the melanoma patients the main tumor lesions were visceral in 18 cases (liver tumors in 8

Table 1 Patients' characteristics

Malignant melanoma patients:	
Eligible patients (*n*)	24
Sex(M/F)	11/13
Median age (range)	59 (43–61) years
WHO performance status:	
0	10
1	10
2	4
Prior treatment:	
Surgery (curative/palliative)	18/4
Radiotherapy	1
Chemotherapy[a]	4
Immunotherapy	1
Renal cancer patients:	
Eligible patients(*n*)	6
Sex(M/F)	4/2
Median age (range)	50 (43–61) years
WHO performance status:	
1	6
Prior treatment:	
Surgery	6
Radiotherapy	1
Immunotherapy	2

[a]Adjuvant regional isolated limb perfusion

patients, lung tumors in 8 patients, 2 patients with both) and soft-tissue tumors in 14 (nodes in 7 patients, skin lesions in 4 patients, 3 patients with both); among the renal cancer patients the main tumor lesions were visceral in 5 cases (lung tumors in 4, liver tumors 1, 1 patient with both) and soft-tissue tumors in 4 (nodes). Four of the melanoma patients had received previous chemotherapy as isolated limb perfusions with melphalan; one patient had received immunotherapy; and one, local radiotherapy. Two of the patients with renal cancer had received previous immunotherapy and one patient, radiotherapy.

Antitumor activity

Three of the melanoma patients did not complete the required two cycles of treatment and were considered nonevaluable for response. The reason for discontinued treatment was nephrotoxicity (see below) in two patients and severe nausea and vomiting in one patient. In the remaining 21 evaluable patients there were 2 complete responders after 1 and 4 cycles of treatment, both involving patients with lymph-node metastases, with responses lasting 5 and 14 months, respectively. One patient with lymph-node and liver metastases showed a PR after 2 cycles lasting 6 months, 2 showed minor responses (PR, but not confirmed after 4 weeks), 3 had stable disease, and 13 had progressive disease. In the group of renal cancer patients, two patients were not evaluable for response due to early nephrotoxicity (see below). None of the four evaluable patients achieved an objective response.

Hematological toxicity

All 24 patients with melanoma, who had received a total of 91 cycles of treatment were evaluable for hematological toxicity. Similarly, all 6 patients with renal cancer who had received a total of 17 cycles of zeniplatin were evaluable for hematological toxicity. Table 2 reports the overall incidence of leukopenia, neutropenia, and thrombocytopenia in these two groups of patients. Leukopenia was the main side effect of the zeniplatin treatment, with seven melanoma patients and four renal cancer patients experiencing at least one episode of grade 3 leukopenia. Hematological toxicity was the most common reason for dose reductions and treatment delays. In two patients with melanoma the dose was reduced, and in five cases further treatment was delayed due to hematological toxicity. In one patient, both a dose reduction and a delay were necessary. In one renal cancer patient the dose was delayed due to hematological toxicity.

Table 2 Hematological toxicity[a]

	WHO grades			
	I	II	III	IV
Malignant melanoma patients:				
WBC	3	9	7	0
Platelet	2	0	0	0
Neutrophil[b]	3	2	2	4
Renal cancer patients:				
WBC	0	1	4	1
Platelet	0	3	0	0
Neutrophil	0	1	3	4

[a]Maximal toxicity per patient
[b]14 patients were not evaluable

Nonhematological toxicity

The main subjective side effect of zeniplatin was nausea and vomiting. Of the 24 patients with melanoma and renal cancer, 27 experienced nausea and vomiting of WHO grade 2 or higher, although almost all patients received prophylactic antiemetic treatment (Table 3). Drug fever and diarrhea were also noted in some patients. One of the patients with renal cancer experienced reversible WHO grade 2 deafness, which occurred 19 days after the first zeniplatin treatment and resolved within 8 weeks.

Nephrotoxicity

In two renal cancer patients, severe nephrotoxicity was observed after the second zeniplatin injection. In one of the patients a rise in the serum level of creatinine was noted at 7 days after the injection, the value increasing from 104 to 1,094 μmol/l. Despite dialysis the patient died. In the other patient a rise in serum creatinine was noted at 3 days after the injection, the level increasing from 88 to 274 μmol/l. Dialysis was not required and the kidney function recovered partially during the next 3 months. At the same time this patient developed a transient, mild case of proteinuria and hypertension,

Table 3 Nonhematological toxicity[a]

	WHO grades			
	I	II	III	IV
Malignant melanoma patients:				
Nausea/vomiting	3	6	8	1
Drug fever	1	4	0	0
Diarrhea	7	0	0	0
Nephrotoxicity	3	0	1	0
Renal cancer patients:				
Nausea/vomiting	0	2	4	0
Drug fever	0	0	0	0
Diarrhea	1	1	1	1
Nephrotoxicity	0	1	1	0
Deafness	0	1	0	0

[a]Maximal toxicity per patient

which gradually returned to normal during the next 3 months.

After serious nephrotoxicity had been observed the trial was temporarily suspended and both protocols were amended to include prehydration. A minimum of 1.5 l of normal saline was given before the zeniplatin infusion, and the urinary output was closely monitored after treatment. The study was reopened only for patients with malignant melanoma, remaining closed for the renal cancer patients since they had frequently undergone a nephrectomy and it was considered that patients with one kidney were at greater risk of developing nephrotoxicity during zeniplatin treatment.

Despite the prehydration, however, one of the melanoma patients developed severe nephrotoxicity, with the serum level of creatinine increasing from 83 to 647 μmol/l on day 16 of the first cycle of zeniplatin. Dialysis was not required, and the creatinine value gradually normalized during the next 2 months. Smaller increases in serum creatinine were also observed in conjunction with the zeniplatin treatment in three other patients with melanoma, two of whom had received prehydration. The creatinine levels increased from 72 to 146 μmol/l, from 92 to 148 μmol/l, and from 91 to 141 μmol/l, respectively, after zeniplatin therapy.

The nephrotoxicity usually occurred during the first two treatment cycles. However, one patient, whose serum creatinine level had remained unchanged during the first five cycles, experienced an increase from 72 to 146 μmol/l in serum creatinine after the sixth cycle, during which the patient had received antiemetic treatment with ondansetron (Zofran) for the first time.

Discussion

The results of the present phase II study in 21 evaluable patients with malignant melanoma demonstrated an overall objective response rate of 14%, with two patients achieving a CR and one patient, a PR. The dose-limiting toxicity of zeniplatin was leukopenia, whereas nausea and vomiting were the main nonhematological side effects. The response rate observed was modest but comparable with the rates obtained in other studies testing cisplatin single-drug treatment in advanced malignant melanoma [2].

No antitumor activity was seen in the renal cancer patients. However, since the study was stopped after only six patients had been included, no conclusion can be drawn regarding the antitumor activity of zeniplatin in this malignancy. Although the drug had shown some antitumor activity in the malignant melanoma patients, the trial was closed before the required number of patients had been included due to the unpredictable and occasionally severe nephrotoxicity of zeniplatin. Also, other ongoing phase II studies have been closed for this reason (American Cyanamid Corporation, personal communication).

The observed nephrotoxicity was unexpected. Animal studies had shown that zeniplatin was less nephrotoxic than cisplatin and had a safety profile similar to that of carboplatin [3]. In several phase I and phase II studies of zeniplatin, no change in serum creatinine values was registered, although many of these patients had previously received nephrotoxic chemotherapy regimens [4, 9]. In the present study, nephrotoxicity was initially seen in renal cancer patients, patients who had undergone nephrectomy. Later, however, it also appeared in the patients with malignant melanoma. Even after prehydration procedures identical to regimens used during cisplatin treatment, new cases of serious nephrotoxicity continued to occur. Indeed, in some cases, zeniplatin nephrotoxicity seemed a more difficult clinical problem than cisplatin nephrotoxicity.

A possible explanation for the unexpected nephrotoxicity may be drug interactions. The renal cancer patient with fatal nephrotoxicity had received one previous zeniplatin cycle without developing any nephrotoxicity. During the second cycle, when the severe toxicity occurred, the patient had received antiemetic treatment with ondansetron for the first time. In one of the melanoma patients it was observed that after five zeniplatin cycles, all of which were well tolerated, the serum creatinine value increased immediately after the sixth cycle, when ondansetron had been given for the first time. Indeed, of the 4 patients who had received concurrent ondansetron, 3 experienced some nephrotoxicity, whereas only 1 of the 20 patients who had not been treated with ondansetron experienced nephrotoxicity.

Worldwide a total of 308 patients have been treated with zeniplatin in different phase II studies. Of these, 32 patients received prophylactic ondansetron, and 14 (44%) of these experienced nephrotoxicity. A total of 276 patients have been treated with antiemetics other than ondansetron, and of these, only 3% (8/276) experienced nephrotoxicity ([1]; American Cyanamid Corporation, personal communication). These data may suggest that ondansetron can contribute to the nephrotoxicity of zeniplatin, but at this stage, no firm conclusion can be drawn regarding the possibility of a drug interaction.

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