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Zeniplatin in Patients with Advanced Ovarian Cancer, a Phase II Study with a Third Generation Platinum Complex

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25 patients with residual or recurrent ovarian cancer were treated with the new platinum complex zeniplatin (CL 286,558) and 23 patients were evaluable for response. Responses were achieved in 4 patients, 1 complete and 3 partial remissions (16%). 7 patients had stable disease and 12 patients had tumour progression. At a median follow-up of 12 months, the median progression-free survival in responding patients was 11 months and overall survival 81%. The median overall survival of progressive patients amounted to 9 months, indicating the advanced stage of disease in most patients. Renal function was monitored by isotope clearance studies. There was no significant change in effective renal plasma flow (ERPF) or glomerular filtration rate (GFR) in 10 patients who completed six cycles of treatment. 1 patient with a marginal creatinine clearance at baseline suffered from sudden and severe renal failure during the first cycle. Zeniplatin may be active in relapsing, platinum-pretreated patients, and has no direct effects on renal function as measured by isotope clearance. Despite these findings, occasional nephrotoxicity may occur in patients with compromised kidney function, even with prophylactic hydration, and thus limit the application of this new analogue.
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INTRODUCTION

THE MAINSTAY of treatment for advanced ovarian cancer over the past 10 years has been systemic chemotherapy with cisplatin-based combinations [1–3]. Several trials have demonstrated that a two-drug schedule is equivalent in terms of response rates and survival to three or four drug combinations [4, 5]. More recently, combinations of carboplatin and cyclophosphamide have shown equivalent survival when compared with cisplatin combinations [6, 7].

The use of cisplatin-containing regimens in the treatment of advanced ovarian cancer entails significant morbidity for the patient. To prevent nefrotoxicity, prolonged prehydration and admission of the patients are required. Vigorous antiemetic regimens have to be employed to control nausea and vomiting associated with cisplatin [8]. Other problems include ototoxicity, central and peripheral neuropathy [9], hypomagnesemia and anaphylactoid reactions, which may be life threatening. The use of carboplatin carries the problem of more myelotoxicity but less neurotoxicity [6]. Clearly, a platinum analogue of equal efficacy and reduced toxicity compared with the parent com-

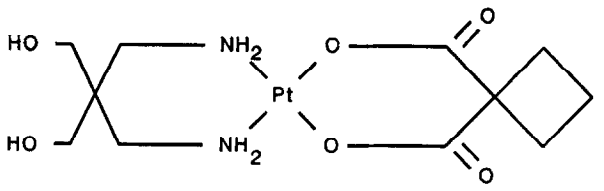

Fig. 1. Structure of zeniplatin (CL 286,558).

pound or with less bone marrow toxicity compared with carboplatin would have an advantage in the treatment of advanced ovarian cancer.

We performed a phase II study with zeniplatin (CL 286, 558), a third generation platinum compound with the chemical structure as shown in Fig. 1. The dose-limiting toxicity of zeniplatin in a phase I study was myelosuppression, especially leucopenia in heavily pretreated patients [10]. Nausea and vomiting occurred often without standardised antiemetics. WHO grade 2 alopecia, grade 2 mucositis, diarrhoea and transient rise in blood pressure occurred sporadically. No ototoxicity or consistent changes in renal function tests were signalled. Based on phase I study, the recommended dose for phase II trials was 120 mg/m^2 once every 21 days.

Responses in phase I trial were seen in 1 patient each with melanoma and renal cell cancer. There have been preliminary reports of phase II studies in non-small cell lung and breast cancer [11–13]. Because ovarian carcinoma is considered to be responsive to platinum analogues, a phase II study was performed in patients who had relapsed or had residual tumour after first line treatment with a cisplatin or carboplatin comprising regimen.

PATIENTS AND METHODS

Patients 18–70 years of age with measurable lesions and disseminated ovarian cancer, were treated with zeniplatin, provided that bone marrow reserve (leucocyte count $> 4.0 \times 10^9$/l and platelets $> 100 \times 10^9$/l), liver (bilirubin < 25 μmol/l) and renal functions were sufficient (creatinine clearance > 60 ml/min). In the first 15 patients, zeniplatin was given without prehydration. Thereafter, all patients received prehydration with 1000 ml normal saline over 2 h, before they were to receive zeniplatin 120 mg/m^2 dissolved in 5% dextrose, infused over 90 min. Patients received 2 l normal saline over 12 h following infusion, and were discharged the next day. As all patients needed antiemetics, they received prophylactic chlorpromazine 25 mg intravenously together with prehydration and 20 mg metoclopramide suppositories every 6 h thereafter.

Dose modification was as follows: for a leucocyte nadir $< 2.0 \times 10^9$/l or platelets $< 75 \times 10^9$/l, drug dose was reduced to 75% and to 50% on repetition; and for a leucocyte count $< 3.0 \times 10^9$/l or platelets $< 100 \times 10^9$/l on day one, the next cycle was postponed for 1 week.

Tumour evaluation was performed every two cycles according to WHO criteria. Patients were removed from the study for severe WHO grade 3–4 non-haematological toxicity or tumour progression. A maximum of six cycles was given. Toxicity was measured according to the WHO criteria after every cycle. Audiograms were performed after every second cycle.

A possible subclinical effect on renal function was measured by double isotope clearance; before every cycle, the effective renal plasma flow (ERPF) by [^{131}I]hippuran clearance and the glomerular filtration rate (GFR) by [^{131}I]PAH clearance [14–16]. Measurements were limited to the first 15 patients and could repeatedly be measured for six cycles in 11 patients.

The study was approved by the local ethical committee and all patients gave informed consent.

RESULTS

Patients' characteristics

The median age of the 25 patients taking part in this study was 54 years, range 37–69 years. 11 patients were previously treated with one chemotherapy schedule (carboplatin plus cyclophosphamide). 7 of these patients had previously achieved a partial remission with residual tumour measuring more than 2 cm. The remaining four had relapsed after a complete remission lasting 15–25 months. 14 patients had received two regimens previously (carboplatin/cyclophosphamide followed by intraperitoneal cisplatin with etoposide intravenously). 2 patients had achieved a partial remission, and 12 had relapsed after a complete remission lasting 5–25 months.

All patients had a good performance status (WHO grade 0–1). 2 patients had grade 1–2 peripheral neuropathy from previous cisplatin treatment. 11 patients received six cycles of zeniplatin (Table 1). 12 patients received less than six cycles due to tumour progression. 2 patients who received only one cycle were considered not evaluable: one patient developed acute renal failure, the other patient had early tumour progression.

Laboratory abnormalities

Two-thirds of a total of 102 cycles were given in full doses. 1 week delay due to leucopenia occurred in only 15 cycles (15%), eight cycles after 100% dosage and seven cycles after 75% dosage of the prior cycle. The most frequent laboratory abnormality included mild leucopenia, with grade III leucopenia occurred

Table 1. Patients' characteristics

Total number	25
Age	
Median (years)	54
Range (years)	37–69
WHO performance status	
Grade 0	23
1	2
Prior chemotherapy	
One schedule	11
Two schedules	14
Number of cycles	Number of patients
1	2
2	6
3	1
4	5
5	—
6	11
Total	25

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Table 2. Leucopenia related to dose given (% of cycles)

	WHO grade				Total number of cycles
	0	1	2	3	
Full dose	18	11	57	14	67
75% dose	26	17	43	14	23
50% dose	66	34	—	—	12

only in 13% of cycles that were given at full dose (Table 2). No patient experienced grade IV leucopenia. Leucopenia appeared to be dose related, as grade II–III leucopenia was found in 71% of fully dosed cycles and 42% of reduced cycles ($\chi^2 = 6.0$, $P < 0.025$) (Table 2). No leucopenia-related fever occurred. Thrombocytopenia was found after eight dose cycles in 5 patients, namely WHO grade I (one cycle), grade II (four cycles), grade III (three cycles). There were no changes in liver enzymes or other laboratory parameters.

Clinical events

3 patients had fever up to 39°C 1–3 days after infusion of zeniplatin, probably resulting from the drug itself. Nausea and vomiting posed problems as all patients experienced grade II–III toxicity after the day of infusion, which lasted for up to 3 days despite prophylatic anti-emetics. Ondansetron was not given to any patient except one. This patient has also received cotrimoxazole for a concomitant urinary infection and had experienced persistent vomiting for 1 week after the first cycle of zeniplatin. When she was readmitted to the hospital, severe renal failure had developed, with a serum creatinine of 1554 μmol/l and creatinine clearance of 5 ml/min. Postrenal obstruction was excluded by sonography. This patient had a marginal creatinine clearance at baseline (65 ml/min). In the past, she had presented with bilateral ureter obstruction and had deterioration of renal function after cisplatin. Dialysis was not started in view of the palliative intent of treatment. She recovered slowly over the course of several weeks with additional hydration and correction of electrolytes. She was discharged after 6 weeks and died 9 months later due to tumour progression.

There were no signs of neurotoxicity. Repeated audiograms remained normal in patients who received a maximum of six cycles of zeniplatin. Diarrhoea was not a problem, nor did significant alopecia occur in the patients treated for this period.

Clinical response

23 patients were evaluable for response, as 2 patients did not receive more than one cycle due to renal toxicity [1] and early progression [1]. Responses were achieved in 4 patients: 1 patient achieved a complete response (CR) and 3 patients achieved a partial remission (PR), which lasted for 7+, and 6, 10 and 11 months, respectively. 7 patients had achieved stable disease after six cycles. At a median follow-up of 12 months in responding patients the median survival is not reached yet, amounting to 81% at a maximal follow-up of 24 months. The median overall survival in progressive patients was 9 months and 10 months in all 23 patients together.

Zeniplatin was most active in patients who had experienced a response to chemotherapy in the past: 9 out of 11 non-progressive patients had achieved a response to prior chemotherapy lasting more than 12 months, while only 2 out of 12 patients with progressive disease had achieved a prior response of this duration ($P < 0.01$ by Wilcoxon test). Prior chemotherapy had no effect on response, as 7 out of 11 responding patients had received two prior chemotherapy schedules vs. 6 out of 12 progressive patients.

Renal function tests

In 11 patients GFR and ERPF were followed over six cycles. 1 patient had a fall in her renal function due to unilateral ureter obstruction by progressive tumour growth after six cycles. In the other 10 patients there was no significant change of GFR or ERPF after six cycles of treatment (Fig. 2). There were no consistent changes in blood pressure before subsequent treatment cycles.

DISCUSSION

This phase II study of zeniplatin in patients with recurrent ovarian cancer has shown that zeniplatin may be effective as second- or even third-line treatment, but preferably in patients who have chemotherapy-sensitive tumours, with a treatment-free interval of over 12 months duration. Thus far, no other

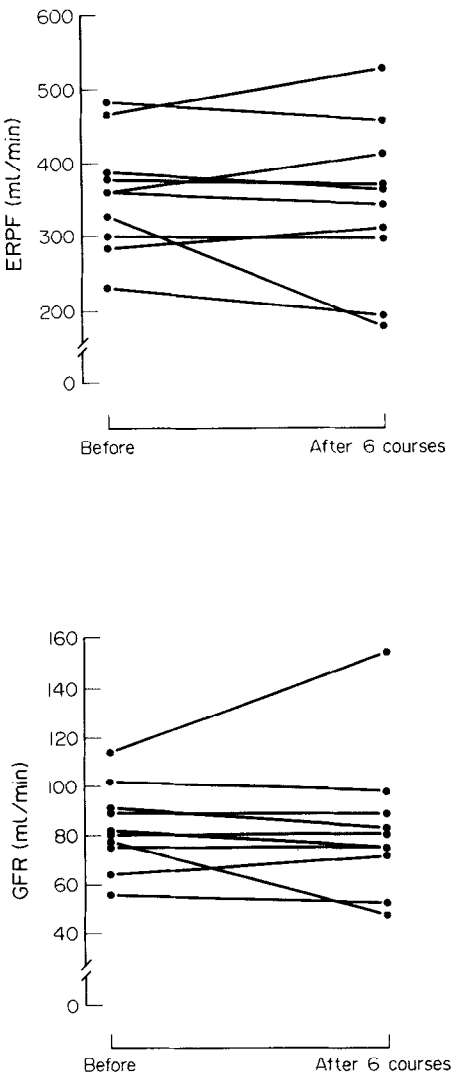

Fig. 2. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in 10 patients before and after six cycles of zeniplatin (NS). (1 patient who developed ureteral obstruction by progressive tumour was omitted.)

platinum analogues have been found that are effective in cisplatin-resistant ovarian cancer. The amount of pretreatment was of little influence, as 4 out of 11 responding patients had received one prior schedule vs. 6 out of 12 progressive patients (not significant).

The main toxic effect of zeniplatin was on the bone marrow, specifically inducing leucopenia and only mild thrombocytopenia, which was short-lived and easy to handle. Leucopenia appeared to be dose dependent, as it was more prominent in fully dosed cycles. Delays of more than 1 week were not necessary, indicating a swift marrow recovery. There were no indications for cumulative marrow toxicity.

The fever that occurred in 12% of patients 1–3 days after infusion was unusual. Its exact cause is unclear, as no other anaphylactoid symptoms were reported. Nausea and vomiting were a problem as conventional antiemetics were often insufficient.

The toxicity profile of zeniplatin appears easy to manage, except for the infrequent occurrence of renal effects. It is doubtful if this can be prevented by adequate prehydration, which was given to the patient who demonstrated renal toxicity. However, this patient had a number of other untoward factors, such as dehydration, urinary infection treated by sulphates, and a pre-existent compromised renal function due to ureter obstruction and prior cisplatin treatment. It should be noted that all the isotope clearance studies were limited to patients who did not receive prehydration. Electrolyte changes indicating tubular damage were not found in this study. The phase I study with zeniplatin mentions reversible renal toxicity at 76 and 100 mg/m^2 [10]. The pharmacokinetics of zeniplatin are similar to those of carboplatin [11], therefore a rapid renal clearance is to be expected. Another phase II study also mentions nephropathy with zeniplatin at a dose of 145 mg/m^2 without prior hydration in a patient with non-small cell lung cancer [12]. The main toxicities encountered in a third phase II study in patients with breast cancer were nausea and vomiting with zeniplatin at a dose of 120 mg/m^2 [13].

We have found no deterioration of renal function measured by isotope clearance in 10 patients treated with six cycles of zeniplatin. Isotope clearance has been shown to be a very reliable method of detecting cumulative nephrotoxicity for other platinum analogues [14, 15]. The unpredictable effect on the kidney in 1 patient with compromised renal function may indicate a different mechanism of toxicity in this patient.

CONCLUSIONS

The conclusions of this phase II study in pretreated patients are as follows: zeniplatin appears effective as a second line treatment in chemotherapy-responsive patients with ovarian cancer. Also, measurement of isotope clearance did not show renal toxicity for zeniplatin over six cycles in 10 evaluable patients. Finally, concomitant or prior treatment with drugs of nephrotoxic potential or dehydration caused by persistent vomiting in patients with compromised renal function may lead to unexpected renal toxicity during treatment with zeniplatin.

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