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A phase II and pharmacokinetic study of enloplatin in patients with platinum refractory advanced ovarian carcinoma

Andrzej P Kudelka, Zahid H Siddik, Damrong Tresukosol,[1] Creighton L Edwards, Ralph S Freedman, Timothy L Madden, Ram Rastogi,[2] Mary Hord, E Edmund Kim, Carmen Tornos, Rosario Mante and John J Kavanagh

The University of Texas MD Anderson Cancer Center, Section of Gynecologic Medical Oncology, 1515 Holcombe Boulevard, Houston, TX 77030-4095, USA. Tel: (+1) 713 792-7959; Fax: (+1) 713 745-1541. [1]Chulalongkorn University Hospital, Bangkok, Thailand. [2]American Cyanamid Company, Pearl River, NY 10965, USA.

This was a study of enloplatin in 18 evaluable patients with platinum refractory ovarian cancer. They received an i.v. infusion of enloplatin over 1.5 h without prehydration every 21 days. One patient had a partial response (6%; 95% CI 0–26%) lasting 2.8 months. The median survival was 9.4 months (95%; CI 5.1–19.7%). Neutropenia was the dose-limiting toxicity. Nephrotoxicity was manageable. Enloplatin is the major form of the free drug in plasma. However, 13.5 h after initiation of treatment, 85% of the drug in plasma is protein bound. Elimination of the drug is mainly renal. Enloplatin pharmacokinetics is similar to that of carboplatin. Thus, the plasma pharmacokinetics of enloplatin is dictated by the cyclobutanedicarboxylato (CBDCA) ligand and not the novel amino ligand.

Key words: Enloplatin, CBDCA, cyclobutanedicarboxylato, ovarian cancer, pharmacokinetics.

Introduction

The development of an organoplatinum compound that has no cross-resistance with carboplatin or cisplatin has been a major goal in the search for new chemotherapeutic drugs. In the treatment of ovarian cancer, the first generation cisplatin and the second generation carboplatin are the mainstay of treatments for patients with advanced ovarian cancer. These compounds have increased complete response rates and extended the disease-free interval since their introduction into the ovarian cancer clinic.[1] Although cisplatin and carboplatin are therapeutically equivalent,[2–5] carboplatin is less nephrotoxic and neurotoxic, and causes less nausea and vomiting than cisplatin. Carboplatin can be administered in an outpatient setting without the need for intensive hydration.[2–5] Dose-limiting toxicity of carboplatin is myelosuppression, particularly thrombocytopenia. As a result of these different serious untoward side effects and the existence of cross-resistance between these two drugs, new drugs of comparable activity, different dose-limiting toxicity or, most importantly, having limited cross-resistance with cisplatin and carboplatin are sought.

Enloplatin, CL287,110; '1,1-cyclobutanedicarboxylato(2-)-*O*,*O*1:(tetrahydro-4*H*-pyran-4,4-dimethanamine-*N*,*N*1)platinum (Figure 1), is a water-soluble third generation platinum analog, that was associated with a relatively low incidence and severity of nausea and vomiting, neurotoxicity, nephrotoxicity, and ototoxicity in clinical phase I trials.[6,7] Enloplatin demonstrated antitumor activity against cisplatin-resistant cell lines *in vitro*, in nude mice and in a phase I study.[6,7] This prompted us to initiate a clinical trial in patients with platinum refractory ovarian cancer to determine its efficacy, adverse event profile and pharmacokinetic characteristics in this patient population.

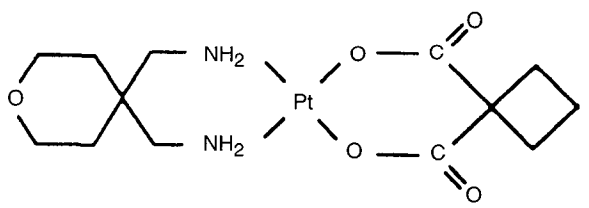

Figure 1. Structural formula of enloplatin.

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Correspondence to AP Kudelka

Material and methods

The eligibility criteria included the following: a histological diagnosis of ovarian epithelial cancer; at least 18 years of age; inoperable, recurrent or metastatic platinum refractory disease; no previous allergic reaction to cisplatin or carboplatin; a Zubrod performance status of 0–2; presence of a bidimensionally measurable lesion (determined by clinical or radiological methods); life expectancy greater than 3 months; no history of other prior malignancy; a neutrophil count greater than 1500/μl; platelet count greater than 100 000/μl; a total bilirubin less than 2 mg/ml; a serum creatinine concentration less than 2.0 mg/ml; and no evidence of ureteral obstruction by tumor. Informed consent was obtained from all patients.

The definition of platinum resistance utilized for our study was based on that proposed by Markmann[8] as follows: (i) disease progression while on platinum-based therapy; or (ii) incomplete response (partial response or stable disease), with persistent macroscopic disease, after six cycles of adequate doses of platinum-based therapy; or (iii) measurable relapse within 6 months of achieving a complete response after platinum-based therapy. Serological relapse alone would not fulfill this criteria. Patients who relapsed after 6 months were considered potentially platinum sensitive.

Treatment regimen

Enloplatin was administered over 1.5 h by contrast i.v. infusion without prophylactic prehydration every 21 days. The first four patients received enloplatin at a dose of 700 mg/m^2. One dose escalation to 900 mg/m^2 was permitted for those patients who tolerated the initial dose of 700 mg/m^2. Each patient was followed for objective and subjective adverse reactions for one full cycle. If no serious adverse reaction was observed, then the next four patients were to be assigned to the 900 mg/m^2 dose level. If there was no serious adverse reaction, subsequent patients were enrolled at 1–3 week intervals. Non-steroidal anti-inflammatory drugs (NSAIDs) and ondansetron as well as hydronephrosis were prohibited due to concern over nephrotoxicity. When ondansetron was used at the initiation of a previous phase II study, three patients developed severe renal insufficiency (data on file with American Cyanamid Company). This was not seen in phase I studies where ondansetron was not used. That phase II study was terminated. In addition to ondansetron use, these patients had some hydronephrosis without changes in serum creatinine. Routine antiemetic therapy (e.g. prochlorperazine, lorazepam, dexamethasone) was given. Prophylatic hydration was not required.

In order to assess the effect of the drug on renal function and drug-related nephrotoxicity, creatinine and creatinine clearance were measured at days 1 (as baseline), 8 and 15 on the first cycle of treatment, and then prior to each following course. Creatinine clearance was calculated based upon a modified Cockroft–Gault prediction using serum creatinine and adjusted for age, weight and gender (i.e. [(140 − age) × weight(kg)]/[serum creatinine (mg/l) × 72]; multiplied by 0.85 for women) or by means of 24 h urine collection.[9] Where possible, plasma clearance of [^{99m}Tc]DTPA was used to further assess glomerular filtration rate (GFR).[10,11]

Subsequent dose modifications were based on the following evidence of both renal and hematologic toxicity on day 1 of each cycle: if a serum creatinine increased to more than 2.0 mg/dl, a 24 h urinary creatinine clearance was obtained. If the creatinine clearance was less than 60 ml/min, then treatment was withheld until values returned to 60 ml/min or greater and a dose reduction to 75% of the prior dose was required. If a granulocyte count nadir was less than 500 cells/μl or platelet less than 50 000 cells/μl, drug dose was reduced to 75% and if it recurred on the next cycle it was reduced to 50% of starting dose: the next cycle was postponed until granulocyte and platelet counts recovered to more than 1500 and 100 000 cells/μl, respectively.

Clinical response assessment

Response status was determined after each course of therapy. Lesions that required imaging studies were measured before every third cycle. Definition of clinical response was based on the following WHO criteria:[12] clinical complete response, defined as complete disappearance of all clinically measurable/evaluable disease, and a normalized level of CA-125; clinical partial response, defined as a 50% or greater decrease in the sum of the products of cross-sectional diameters of all measurable lesions; stable disease, defined as any condition other than objective response or progressive disease; progressive disease, defined as a 25% or greater increase in the sum of the products of the cross-sectional diameters of all measurable lesions and/or the development of new lesions; response duration was measured from the time of maximal response (not beginning of treatment) until there was evidence of progression.

Determination of enloplatin concentrations. Blood specimens (2–10 ml) were collected before drug administration, and at several time points during and after drug administration. Urine was collected continuously beginning pre-dose and ending up to 4 days after the start of drug infusion. All specimens were cooled immediately on ice. The major part of the blood specimen was centrifuged at 1500 *g* for 10 min at 4°C and the plasma separated. Aliquots of the plasma (0.5–1.0 ml) were transferred immediately to Amicon Centrifree micropartition tubes, which were centrifuged at 2000 *g* for 60 min at 4°C to prepare plasma ultrafiltrates (PUF). All specimens were stored at −70°C. Chromatography for unchanged enloplatin in PUF was performed on a Waters high pressure liquid chromatography (HPLC) system, using a Hypersil ODS (C_{18}) reverse-phase column (250 mm × 4.6 mm) with a 20 mm × 2 mm C_{18} guard column. The column was eluted at 1.0 ml/min with a mobile phase consisting of $NH_4H_2PO_4$:methanol:2-propranol (910:85:5; v/v) and enloplatin was detected by u.v. absorption at 230 nm. The drug eluted with a retention time of about 10.5 min. Standard curves for concentrations of 0.25–100 μg/ml were used to determine drug levels in the specimens. Total platinum levels in blood, plasma, PUF and urine were determined by flameless atomic absorption spectrophotometry (FAAS).[13,14]

FAAS was performed on a computer-controlled Varian AA300 atomic absorption spectrophotometer equipped with a GTA96 graphite furnace atomizer. Detection was at 265.9 nm using deuterium background correction. Quantitation was by the method of standard addition to correct for matrix effects.[13,14] Total platinum was converted to total enloplatin equivalents.

Pharmacokinetic analysis. Standard principles and approaches were used in the non-compartmental pharmacokinetic evaluation.[15] The peak plasma concentration (C_{max}) was determined by visual inspection of the plasma concentration versus time data. The terminal slope (K) was determined by best fit least-squares regression analysis of the terminal log-linear portion of the log plasma concentration versus time profile using the last three to five data points. The area under the plasma concentration versus time curve (AUC_{0-T}) from time 0 to time T of the last reportable drug concentration (C_T) was determined by using the linear trapezoidal rule up to C_{max} followed by the log trapezoidal method at subsequent time-points. AUC from time 0 to infinity ($AUC_{0-\infty}$) was estimated by the sum of AUC_{0-T} and C_T/K. The systemic clearance (CL_T) was determined from the quotient of dose and $AUC_{0-\infty}$. V_{ss} (the volume of distribution at steady state) was calculated using the following equation:

$$V_{ss} = \frac{\text{infused dose} * \text{AUMC}}{(\text{AUC})^2} - \frac{\text{infused dose} * \tau}{\text{AUC} * 2}$$

where τ is the time of infusion and AUMC is the area under the moment curve. AUMC from time 0 to T ($AUMC_{0-T}$) was estimated by the trapezoidal method with the same criteria as for AUC_{0-T}. The AUMC from zero to affinity ($AUMC_{0-\infty}$) was calculated by:

$$\text{AUMC}_{0-\infty} = \text{AUMC}_{0-T} + \frac{t * C_T}{K} = \frac{C_T}{K^2}$$

The effective half-life ($T_{1/2}$) of the drug was calculated as the product of the mean residence time (MRT) and 0.693, where MRT is the quotient of $AUMC_{0-\infty}$ and $AUC_{0-\infty}$.

Results

Clinical effects

Twenty-one patients were entered: the median age was 57 years (range 42–75) and median Zubrod performance status was 1 (0–2). Eighteen patients (84%) were evaluable for response (Table 1). All patients were previously treated with platinum-based chemotherapy. Seventeen had clinically documented platinum-resistant disease and one relapsed 9 months after achieving a complete response on previous platinum-based chemotherapy. Eight patients had received paclitaxel and five docetaxel prior to enrollment into our study. There was one partial response

Table 1. Patient characteristics

Evaluable	18
Inevaluable	3
Age (years)	57 (42–75)
Zubrod	1 (0–2)
Histology	
papillary serous	14
mixed epithelial	4
mucinous	1
clear cell	1
adenocarcinoma	1
Grade	
1	1
2	1
3	19
Prior chemotherapy	21
median no. of regimens (range)	4 (1–6)
paclitaxel	8
docetaxel	5
Prior radiation	3

(6%, 95% CI 0–26%) lasting 2.8 months (Table 2). Five evaluable patients (28%; 95% CI 9–54%) had stable disease with a median of 4 months (range 2–8.3) to progression. Three patients progressed after the first course and were removed from study. Three were inevaluable since they were lost to follow-up before completing two courses. The median number of courses was 2 (range 1–14). Six patients received a dose escalation while eight required a dose reduction. The median survival of all the evaluable patients was 9.4 months (95%; CI 5.1–19.7%) (Figure 2). The only responder in the trial had two prior regimens. She received four courses of enloplatin, one course at 700 mg/m^2 and at 525 mg/m^2, and two courses at 350 mg/m^2.

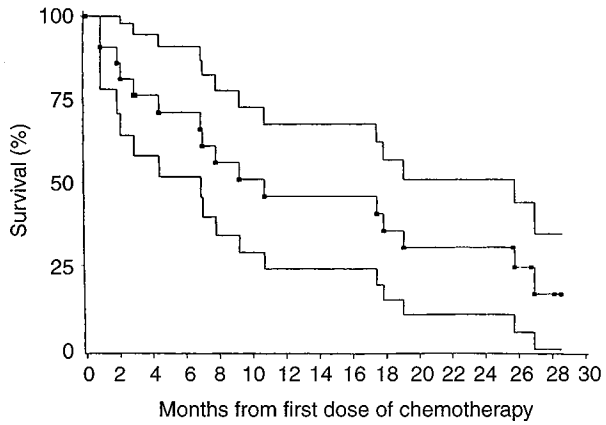

Figure 2. Kaplan–Meier survival curve of patients treated with enloplatin. Mean survival (■)=9.4 months; 95% CI (—)=5.1–19.7 months.

Enloplatin was well tolerated overall (Tables 3 and 4). Neutropenia was the main dose-limiting toxicity. The median nadir granulocyte count was 1218 cells/μl (range 0–5243). Eleven patients (52%) had WHO grade 4 neutropenia, with two occurrences of neutropenic fever that required hospitalization. WHO grade 3 thrombocytopenia was noted in one patient. Three patients developed WHO grade 3 nausea and two patients had WHO grade 4 emesis.

Seven of 18 patients had WHO grade 3 or 4 nephrotoxicity, three had grade 4 and four had grade 3. Of these, one patient had a 65% reduction of creatinine clearance (to 62 ml/min) and a 10% rise in serum creatinine during the first course of therapy. Another patient had progressive disease and hypercalcemia, and a 10% rise in serum creatinine with a 10% fall in creatinine clearance. The remaining 11 patients showed no significant change of renal function or cumulative nephrotoxicity. Furthermore, there were no significant cardiovascular complications, neurologic or ototoxicities noted while on this therapy. Two patients died while on study. One patient developed a pulmonary embolism and the other rapidly progressive disease.

Clinical pharmacology

The enloplatin concentrations or equivalents in blood, plasma and PUF samples from a representative patient are shown in Figure 3. Peak concentrations were seen at the end of drug infusion. Thereafter, the drug decayed biphasically. Plasma concentrations were substantially greater than those in whole blood for

Table 2. Response of evaluable patients

Response	No. of patients	Time to progression (months) [median (range)]
Partial remission	1 (6%, 95% CI 0–26%)	2.8
No change	5 (28%, 95% CI 9–54%)	4.0 (2.0–8.3)
Progression	12	
All	18	1.7 (0.7–8.3)

Table 3. Hematologic toxicities in all 21 patients

Toxicity	WHO grade [no. of patients (%)]			Nadir [Median (range)]
	1,2	3	4	
Neutropenia	3 (14)	3 (14)	11 (52)	1218 (9–5243)/μl
Thrombocytopenia	1 (5)	1 (5)	0	265 (39–396) × 10^3/μl
Anemia	16 (76)	2 (10)	0	10.7 (7.7–13.2) g/dl

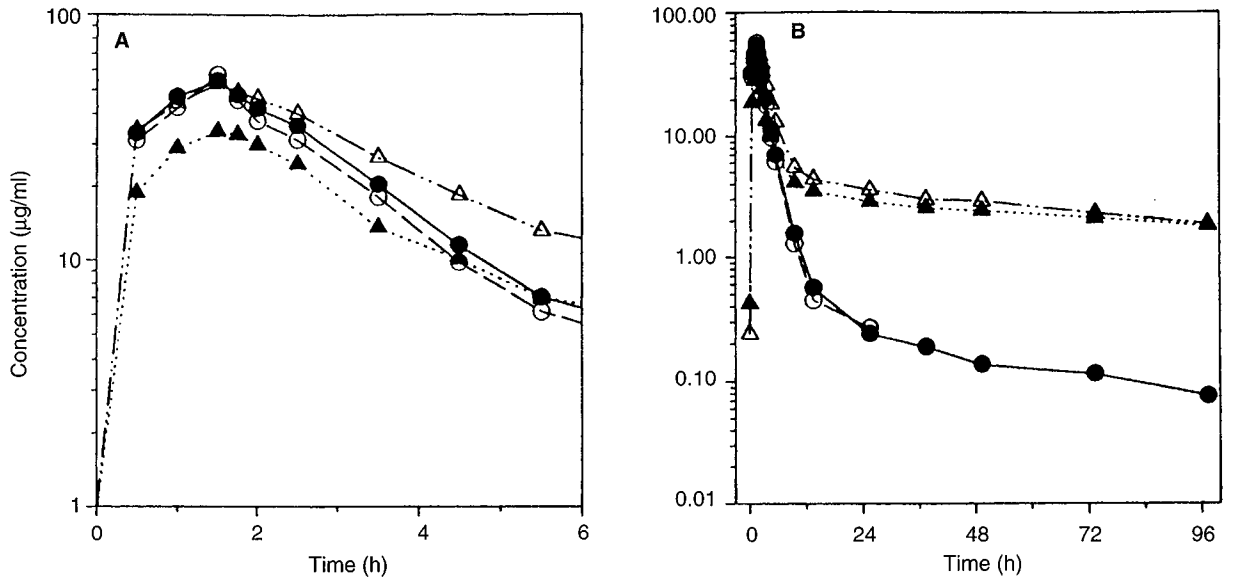

Figure 3. Pharmacokinetics of enloplatin in a patient. (A) Drug levels to 6 h and (B) to 97.5 h. Blood, ▲; plasma, △; PUF (FAAS), ●; PUF (HPLC), ○.

Table 4. Non-hematologic toxicities (moderate and severe)

Toxicity	No. of patients
Diarrhea	3 (14)
Nausea	8 (38)
Emesis	7 (33)
Anorexia	1 (5)
Stomatitis	1 (5)
Decreased creatinine clearance	7 (33)
Fatigue	3 (14)
Other	2 (10)
dygusia during chemotherapy	
numb tongue during chemotherapy	

the first 5.5 h, suggesting that penetration of enloplatin into blood cells was low. With time the levels in blood approached those in the plasma so that after 4 days the levels in the two compartments were similar. Concentration versus time curves for the the lower levels measured by FAAS or HPLC were almost superimposable. This indicated that enloplatin was the major form of the free drug in the plasma. However, the lower level of detection limits precluded estimation of enloplatin by HPLC beyond 24 h in this and two other patients. Detection of enloplatin in PUF was limited to 8 h in one patient and 12 h in four others. Comparison of level in the plasma and PUF provided evidence that up to 2.5 h after initiation of drug infusion the major form of the drug in the plasma was as the intact enloplatin molecule. After this time-point, however, the gradual divergence of the plasma

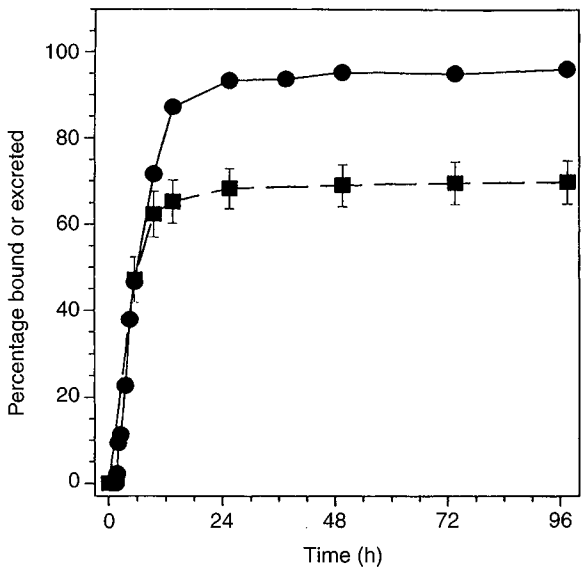

Figure 4. Plasma protein binding (●) and urinary excretion (■) of enloplatin.

and PUF curves was evident (Figure 3) and indicated increasing levels of plasma-bound drug with time, probably arising from an irreversible interaction between enloplatin and plasma proteins. The plasma protein binding calculated from the data in Figure 3 is shown in Figure 4. Protein binding was negligible at the early time-points, but significant binding (more than 10%) was noted after about 2.5 h and by about 13.5 h more than 85% of the drug in the plasma was bound.

Table 5. Mean (CV%) pharmacokinetic parameters for enloplatin (700 mg/m^2) following administration of a single 90 min i.v. infusion during cycle 1 in advanced refractory ovarian carcinoma patients

Matrix	C_{max} (μg/ml)	MRT (h)	$T_{1/2}$ (h)	AUC_{0-t^*} (μg·h/ml)	$AUC_{0-\infty}$ (μg·h/ml)	CL_T (ml/min)	V_{ss} (L)
Whole blood	38 (21)	81 (76)	56 (76)	289 (33)	449 (41)	53 (60)	188 (58)
Plasma	57 (20)	75 (78)	52 (78)	392 (30)	584 (42)	41 (58)	132 (60)
PUF using FAAS	58 (19)	8.3 (43)	5.8 (43)	181 (20)	185 (21)	111 (26)	49 (53)
PUF using HPLC	56 (17)	3.5 (34)	2.4 (34)	158 (22)	161 (23)	127 (24)	20 (21)

t^*=the last time-point at which quantifiable concentration of the drug was present and ranged from 25.5 to 169.5 h.
N=8 patients treated at 700 mg/m^2 with enloplatin.
The values in parentheses represent %CV.

Pharmacokinetic parameters were determined in eight patients using a non-compartmental approach. The values calculated for the pharmacokinetic parameters are presented in Table 5. The parameter values for total drug in blood and plasma for MRT, $T_{1/2}$, V_{ss} or AUC were similar, but greater than those for unbound drug in PUF. The apparent whole blood and plasma clearance of total enloplatin, on the other hand, were less than those for free and unchanged drug in PUF. The $AUC_{0-\infty}$ for free drug in PUF was only 30% of the amount seen in plasma and this is consistent with the clearance of protein-bound drug being slower than that of free enloplatin.

Elimination of the drug was predominantly via the renal route, with 62 and 70% of the administered dose being excreted in the urine at 10 and 97.5 h, respectively (Figure 4). Comparison of the curves in Figure 4 indicates that the rate of urinary excretion was substantial while protein binding was low during the early time-points (less than 10 h), but thereafter decreased progressively with time as the binding increased. As a representation of the GFR, the [^{99m}Tc]DTPA plasma clearance in six patients (90±8 ml/min, mean±SD) was combined with creatinine clearance in two other patients (94 and 115 ml/min) to obtain a mean value of 94±11 ml/min. The renal clearance of the drug, from the ratio of urinary excretion (Figure 4) and CL_T (Table 5) was approximated as 78 ml (by FAAS) and 89 ml/min (by HPLC), which are very similar to the GFR. Together with a reasonable linear regression correlation (r=0.83; p=0.011) between GFR and PUF CL_T (by FAAS), the data suggest that enloplatin clearance was highly dependent on the patient's renal function.

Discussion

This trial was performed based on preclinical evidence that enloplatin shares incomplete cross-resistance with cisplatin and carboplatin.[16] Our result did not confirm preclinical findings and demonstrated that enloplatin has only minimal activity in platinum refractory ovarian cancer. So far, no other platinum analog has been found to be effective against platinum-resistant ovarian cancer. Willemse *et al.*[17] also reported negative results of a phase II trial evaluating the effectiveness of zeniplatin, another third generation platinum analog, in a similar patient population. In the present phase II trial, we found a minimal level of antitumor activity for enloplatin in patients with clinically defined, platinum-resistant ovarian cancer. The results strongly suggest the existence of cross-resistance between the two drugs, albeit incomplete. Therefore, second-line treatment with enloplatin may be worthwhile only in patients without prior evidence of tumor resistant to platinum. The introduction of enloplatin may be considered in patients where thrombocytopenia or neurotoxicity are more of a problem than granulocytopenia. The response to a new drug observed in an individual with documented platinum-resistant ovarian cancer would suggest that the drug may have a mechanism of action somewhat different from that of cisplatin.

Ovarian cancer is one of the more chemotherapy-responsive solid tumors, with objective response rates to platinum-based regimens reported to be between 60 and 80%. However, despite the sensitivity of the tumor to cytotoxic agents, the majority of responding patients ultimately recur with drug-resistant tumor and die of complication of their diseases. Thus, the critical need remains to find new drugs that have major cytotoxic activity against that cell population which is resistant to cisplatin or carboplatin.

The pharmacokinetics of enloplatin was determined as an adjunct to the phase II trial. The pharmacokinetics of the platinum agent is distinctly different from that of cisplatin, which is characterized by a rapid plasma clearance ($T_{1/2}$, 18–37 min; CL_T, 400–600 ml/min) due to extensive irreversible plasma protein binding (below 10% free drug by 4 h) and modest

urinary excretion (16–35% of dose in 24 h).[18,19] In contrast, intact enloplatin was only approximately 40% bound to plasma proteins in 4.5 h after the start of drug infusion and approximately 60% of the dose was excreted in the urine within the first 10 h. Enloplatin pharmacokinetics, however, were similar to that of carboplatin[19,20] with regard to protein binding, urinary excretion, $T_{1/2}$, CL_T, renal clearance/GFR ratio and the volume of distribution. This pharmacokinetic similarity is consistent with both enloplatin and carboplatin possessing the cyclobutanedicarboxylato (CBDCA) ligand, which makes the molecule less reactive toward macromolecules than does the chloro ligand of cisplatin.[19] Thus, the plasma pharmacokinetics of enloplatin is dictated by the presence of the CBDCA ligand and appears not to be influenced by the novel coordinately bound amine ligand. This conclusion is strengthened by the reported finding that the pharmacokinetics of CI-973[21] and zeniplatin,[22] two other CBDCA-containing cisplatin analogs, are also similar to that of carboplatin.

Enloplatin produced manageable nephrotoxicity, lacked significant neurologic and ototoxicity, and induced dose-limiting myelosuppression, which are properties shared with carboplatin,[23] CI-973[21–24] and zeniplatin.[25] This suggests that at least the adverse pharmacodynamic properties of enloplatin, zeniplatin, carboplatin and CI-973 are probably related to their similar chemical reactivities and pharmacokinetic profiles.

Conclusion

The main toxic effects of this dose of enloplatin were myelosuppression and nephrotoxicity. Granulocytopenia was common, dose limiting and generally short lived. Half of the patients experienced grade 4 granulocytopenia. Renal toxicity was common with one-third having grade 3 or 4 severity. The other non-hematologic toxicity seen in this study was encouragingly low, with less neurotoxicity and ototoxicity than might have been found with cisplatin. The degree of granulocytopenia was severe in some patients, but was acceptable, considering the multiple regimens they had received previously. One partial response was observed. The pharmacokinetics of enloplatin was similar to that reported for carboplatin, and therefore determined by the CBDCA and not the amino ligand.

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