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Second-line Treatment of Advanced Measurable Ovarian Cancer with Iproplatin: a Southwest Oncology Group Study

Geoffrey Weiss, Stephanie Green, David S. Alberts, James Tate Thigpen, Harry E. Hines, Karl Hanson, H. Irving Pierce, Laurence H. Baker and John Wendall Goodwin

105 patients with advanced ovarian cancer previously treated with cisplatin or carboplatin were entered into a study of iproplatin as second-line therapy. Patients were either clinically resistant to cisplatin or carboplatin, or had relapsed after complete response to these agents. Patients were treated intravenously at an initial dosage of 270 mg/m^2 with dosage adjustments to 340, 200 or 135 based on observed toxicity. Of 101 eligible patients, 7 responses (3 complete, 4 partial; 12%) were observed in 60 patients resistant to cisplatin. 2 partial responses (11%) occurred in 18 patients resistant to carboplatin. 2 complete and 3 partial responses were observed in 19 patients (26%) previously treated with but not resistant to cisplatin. Response durations were 2–20 months. Toxicities of iproplatin included thrombocytopenia in 93% of patients, leukopenia in 76% of patients, anaemia in 68% of patients, and diarrhoea in 40% of patients. Thus iproplatin shares cross-resistance with cisplatin and carboplatin in the treatment of ovarian cancer and is not recommended as an effective second-line agent for platinum-resistant ovarian cancer.
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INTRODUCTION

OF APPROXIMATELY 18 000 new patients with ovarian cancer diagnosed annually in the United States, two thirds will ultimately die of their malignancy [1]. This high proportion failing to achieve satisfactory control of disease reflects both the tendency for patients with this disease to present in an advanced state and the capacity of advanced disease to acquire resistance to most conventional systemic therapies. Clinical research in the management of advanced ovarian cancer, including cytoreductive surgery, intraperitoneal therapies and multidisciplinary approaches to treatment, seeks to overcome the therapeutic limitations imposed by refractory disease, dose-limiting toxicities of treatment and the marginal activity of existing drugs.

Alkylating agents and cisplatin have long been recognised as representatives of the more active agents in modern combination regimens for advanced ovarian cancer. Cisplatin's well-known gastrointestinal, renal and neurological toxicities have stimulated the search for analogues that are at least equivalently active yet less toxic. Carboplatin was approved for marketing in the USA on the strength of therapeutic equivalence with cisplatin as second-line therapy against advanced ovarian cancer, yet producing substantially less gastrointestinal and renal toxicity [2]. Iproplatin, another second generation analogue, has been undergoing similar evaluation as an alternative to cisplatin.

Iproplatin is more water soluble than cisplatin and has preclinical antitumour activity similar to cisplatin [3]. In phase I and II trials, the dose-limiting toxicity of iproplatin was thrombocytopenia [4, 5]. In previously untreated advanced ovarian cancer, iproplatin produced an overall response rate of 74–78% [6, 7]. In patients with ovarian cancer previously treated with cisplatin, the response rate was 22%, suggesting cross-resistance with cisplatin. In 1985, the Southwest Oncology Group launched a trial of iproplatin in advanced ovarian cancer previously treated with cisplatin or carboplatin. This trial sought

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Table 1. Southwest Oncology Group toxicity criteria

Grade 0	1	2	3
Nausea, vomiting			
Normal	Nausea, no vomiting	Vomiting prevented by treatment; <6 per day	Vomiting despite treatment; > 6 per day
Diarrhoea			
<3 bowel movements per day	3–4 liquid stools per day; no dehydration	>4 liquid stools per day; needs intravenous hydration	Bloody diarrhoea; needs vigorous intravenous hydration or blood

to establish whether such cancer has acquired resistance to iproplatin.

PATIENTS AND METHODS

Patients

Patients enrolled on this study (SWOG 8500) met the following criteria: histopathologically confirmed diagnosis of incurable advanced, metastatic or recurrent epithelial carcinoma of the ovary; failure to attain a complete response on first-line therapy with a cisplatin or carboplatin containing regimen for advanced disease, or demonstrated resistance to platinum containing chemotherapy upon retreatment of previously sensitive disease, or relapse after achievement of a complete response to prior cisplatin or carboplatin containing chemotherapy; bidimensionally measurable disease; SWOG performance status 0–2; pretreatment white blood cell count (WBC) 3500/μl or more, or absolute granulocyte count 1500/μl or more, and platelet count 100 000/μl or more; serum creatinine 1.5 mg/dl or less; urine creatinine clearance 60 ml/min or higher; serum bilirubin 2.0 mg/dl or less; at least 4 weeks since previous therapy and full recovery from all toxicities of previous therapy. All patients gave written informed consent consistent with institutional and federal guidelines.

Treatment plan

The initial dose of iproplatin was 270 mg/m² prepared in 100 ml 5% dextrose in water, administered intravenously over 30 min. Intravenous fluid hydration was not routinely administered before or during treatment. Patients were retreated every 28 days. Patients were retreated at the starting dosage unless toxicity accompanying preceding courses necessitated dosage reduction. In the absence of toxicity in a previous course of treatment (WBC nadir over 3000/μl and platelet nadir over 75 000/μl), a single dosage escalation (340 mg/m²) was permitted. Dosage reduction for toxicity was done according to the following guidelines: dosage was reduced one level for platelet nadir of 25 000–49 999/μl or WBC nadir of 1000–1999/μl in the preceding course; dosage was reduced two levels for platelet nadir below 25 000/μl or WBC nadir under 1000/μl. The first dosage level below the starting dosage was 200 mg/m² and the second dosage level was 135 mg/m². Treatment was discontinued if toxicity requiring dosage reduction occurred at the lowest dosage level. Patients must have fully recovered from the toxicity of the previous course of treatment before administration of any subsequent course, and serum creatinine must have been less than 1.5 mg/dl before administering any course.

An interval CBC was obtained 2 weeks after the preceding course to provide data upon which dosage adjustments were based. X-rays, scans or physical examinations for tumour measurement were done at least after every other course of treatment. Before

Table 2. Patients' characteristics

	No.
Eligible patients	101
Median-age (range) (yr)	57 (26–80)
Performance status-median (range)	1 (0–2)
0	38
1	40
2	23
Previous therapy	
Chemotherapy	87
Radiation/chemotherapy	14
Cisplatin	80
Cisplatin resistant	61
Carboplatin	21
Carboplatin resistant	18

Table 3. Response

	Total patients	CR (%)	PR (%)	Response rate
Previous cisplatin	80	5 (6%)	7 (9%)	15%
Cisplatin-resistant	60	3 (5%)	4 (7%)	12%
Previous carboplatin	20	1 (5%)	2 (10%)	15%
Carboplatin-resistant	18	0	2 (12%)	11%

CR = complete response, PR = partial response.

Table 4. Haematological toxicity

	Courses with toxicity			
Dosage (mg/m²)	340	270	200	135
Leukopenia (/μl)				
3000–3999	9	54	36	16
2000–2999	13	36	39	3
1000–1999	3	13	7	1
Granulocytopenia (/μl)				
1000–1499	1	10	13	1
500–999	1	3	3	0
<500	0	1	0	0
Thrombocytopenia (/μl)				
75 000–99 999	5	15	32	10
50 000–74 999	8	35	30	6
25 000–49 999	10	37	25	8
<25 000	9	30	8	0
Haemoglobin (g/dl)				
9.9–9.0	14	41	30	12
7.0–8.9	9	40	22	7
5.0–6.9	1	5	1	0
<5.0	1	1	1	0
Total courses	41	163	129	53

Table 5. Non-haematological toxicity

	Courses with toxicity			
Dosage (mg/m²)	340	270	200	135
Nausea, vomiting				
Grade 1	4	19	21	13
Grade 2	24	99	57	16
Grade 3	2	15	6	1
Diarrhoea				
Grade 1	7	28	14	8
Grade 2	3	5	0	0
Grade 3	0	1	0	0
Total courses	41	163	129	53

each subsequent course, patients underwent physical examination and check for toxicity of the previous course.

Response and toxicity criteria

The following criteria were used for response in all patients: complete response, complete disappearance of all evidence of malignancy and no evidence of new malignant lesions for at least 6 weeks; partial response, 50% or greater reduction in the sums of the products of the largest perpendicular diameters of measurable lesions for determinations separated by at least 4 weeks; stable disease, failure to meet the criteria for response or progression of disease; and progressive disease, 25% or greater increase in the sum of the products of the largest perpendicular diameters of any measurable lesion or the appearance of new lesions.

The toxicities of patients treated on this trial were monitored and graded according to SWOG criteria (Table 1).

RESULTS

Patients' characteristics

The characteristics of the patients treated on this trial are summarised in Table 2. Of 105 enrolled patients, 4 were ineligible: 2 patients were treated before registration with the Statistical Center, 1 was treated more than 2 weeks after prestudy data were obtained (investigators are required to obtain prestudy data within 2 weeks of enrolment) and 1 had been treated for breast cancer within 5 years of enrolment. 101 patients were eligible to receive treatment, and their experience is the basis for this report.

Median performance status for this group was 1 (range 0–2) and median age was 57 (26–80). 80 patients had received previous treatment with cisplatin, 21 with carboplatin. Of the patients who had received cisplatin, 61 failed to achieve a complete response to initial treatment or to rechallenge with this agent. 1 patient in this group received no treatment due to insurance difficulties and was considered inevaluable. Of the patients who had received carboplatin, 18 failed to achieve a complete response to initial treatment or to rechallenge with this agent.

Response data

100 eligible patients were evaluable for response (1 patient was not treated) (Table 3). 60 patients were clinically resistant to previous cisplatin treatment; of this group, there were 3 complete responses and 4 partial responses (12% overall response rate, 95% CI 5–23%). Among 19 patients previously treated with cisplatin but not shown to be clinically resistant, there were 2 complete responses and 3 partial responses (26% overall response rate, 9–51%). 18 patients were clinically resistant to previous carboplatin treatment. Of this group, there were 2 partial responses (11% overall response rate, 1–35%). Response duration among all responding patients was 4, 5, 6+, 10 and 11+ months for complete responders and 2, 3.5+, 4, 4, 4+, 5, 6, 9+ and 20 months for partial responders.

Toxicity

386 courses of iproplatin were administered to 100 patients. Toxicities at each of the treatment dosage levels are summarised in Tables 4 and 5. The major haematological toxicity accompanying treatment with iproplatin was thrombocytopenia, occurring in 268 courses (70%) in 93 patients (93%). Platelet counts less than 50 000/μl were observed in 127 (33%) of treatment courses in 78 patients (78%). 1 patient died of haemorrhage complicated by severe thrombocytopenia. Leukopenia occurred in 230 (60%) of treatment courses among 76% of patients, only 6% of courses falling below 2000/μl (16% of patients). 33 courses of treatment complicated by leukopenia were also complicated by granulocytopenia (under 1500/μl). 1 granulocytopenic patient died of sepsis. Anaemia (haemoglobin under 10 g/dl) occurred in 185 courses (48%) of treatment in 68 patients (68%). Haematological toxicity was the most frequently observed side-effect, yet was not usually complicated by adverse or symptomatic consequences for the affected patients.

Iproplatin was significantly emetogenic: nausea and vomiting occurring in 277 courses (72%) among 93 patients (93%). Other non-haematological toxicities included (in decreasing order of frequency) diarrhoea (17% of treatment courses), paresthesias (3%), and episodic vertigo, confusion, fatigue, alopecia, rash, stomatitis, hyperbilirubinaemia, atrial fibrillation and creatinine elevation (all 1% or less).

DISCUSSION

This trial was started on the strength of several lines of evidence suggesting that iproplatin shares incomplete cross-resistance with cisplatin and carboplatin. Alberts and coworkers have examined the sensitivity of ovarian cancer specimens from untreated patients and cultured in the human tumour clonogenic assay [8]. Dose-survival curves were constructed over a 3-log concentration range and estimates of the dosages at which 30% of tumour colony forming units survived (ID30) were calculated. In this assay, an ID30 was reached for 77% of tumours treated with cisplatin or carboplatin and for 92% of tumours treated with iproplatin. 75% of ovarian tumours found initially resistant to cisplatin or carboplatin were sensitive to iproplatin.

The EORTC evaluated iproplatin in advanced ovarian cancer and produced an overall response rate of 22% among patients previously treated with cisplatin [6]. Further, those patients with evidence of clinical resistance to cisplatin (failure to respond to cisplatin or relapse while on treatment with cisplatin) produced overall responses of 3.4% and 11%, respectively. Although these response rates were lower in cisplatin-resistant patients than those we found, the confidence intervals for the response rates in our larger population of patients suggest similar levels of activity. Further, this degree of activity for second-line iproplatin was not significantly different from that of second-line carboplatin (response rate 6.5%) in ovarian cancer patients resistant to cisplatin [9].

Blackledge *et al.* have reported characteristics of advanced ovarian cancer patients failing primary chemotherapy that predict response to second-line treatment in phase II studies [10]. In multivariate analysis, the factors that best discriminate those

patients unlikely to respond to second-line therapy include progression of disease on primary therapy or relapse from remission within 3–6 months of conclusion of primary therapy. In our study, the interval between conclusion of previous cisplatin or carboplatin therapy and entry to this study for patients who were resistant to or failed to achieve complete response with primary therapy and ultimately experienced an objective response to iproplatin ranged from 2 months to 47 months (median 15).

This study has demonstrated that iproplatin can induce partial or complete responses in a limited proportion of cisplatin-resistant ovarian cancer patients and of carboplatin-resistant patients. Although response rates were low, it is noteworthy that these anticancer effects occurred in a subset of patients notoriously resistant to any treatment modality. In addition, response duration was appreciable (over 6 months) for several patients. The further clinical development of iproplatin is unlikely due to its modest antitumour activity in other gynaecological malignancies and solid tumours. However, its use as a second-line agent for platinum-complex resistant ovarian cancer might be rationalised in combination chemotherapy regimens with other active agents (e.g., etoposide, mitoxantrone, ifosfamide, and taxol). Iproplatin at this dosage and schedule cannot be recommended as an effective agent alone against platinum-resistant ovarian cancer.

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Distribution of Fenretinide in the Mammary Gland of Breast Cancer Patients

Rajendra G. Mehta, Richard C. Moon, Michael Hawthorne, Franca Formelli and Alberto Costa

Fenretinide has been used orally as a chemopreventive retinoid in a trial for women at risk of developing contralateral breast cancer. The levels of fenretinide and its metabolites were measured in the breast tissue obtained at surgery from women in the trial. Fenretinide was concentrated by breast tissue. Two major metabolites were detected in the tissue extract, one co-eluting with N-(4-methoxyphenyl)retinamide (4-MPR), and the other, more polar, eluting at 17 min under the conditions used. This metabolite remains unidentified. Division of the breast tissue into epithelial cells and fat fractions revealed that fenretinide and the metabolite at the 17 min peak were concentrated in the epithelial cells, whereas 4-MPR was principally localised in the fat compartment. Thus fat may serve as a storage compartment for the retinoid.
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INTRODUCTION

CONSIDERABLE ATTENTION has been directed towards the evaluation of retinoids as chemopreventive agents [1, 2]. Among the chemopreventive retinoids tested, fenretinide N-(4-hydroxyphenyl)retinamide, is the most efficacious in preventing chemically induced carcinogenesis in various target organs. Fenretinide is less toxic than retinyl esters, retinoic acid or any other synthetic retinoid at equimolar concentrations in rodents [3].

Fenretinide is being evaluated clinically for its effectiveness in preventing contralateral breast cancer in stage 1 patients who have received neither hormonal therapy nor chemotherapy. Patients receive 200 mg daily, a dose selected from the phase I