combinations of piperacillin with quinolones. *Pathol Biol* 1988, **36**, 357–360.
14. Ribrag V, Droz JP, Andremont A. Infectious complications associated with granulocytopenia during the treatment of poor risk or relapsed germ cell tumors. *Bull Cancer* (submitted).
15. Chek C, Oppenheim B, Anderson H, Swindell R, Scarffe H. Randomized trial comparing ciprofloxacin plus netilmicin versus piperacillin plus netilmicin for empiric treatment of fever in neutropenic patients. *Antimicrob Agents Chemother* 1989, **33**, 87–91.
16. Bregman C, Williams P. Comparative nephrotoxicity of carboplatin and cisplatin in combination with tobramycin. *Cancer Chemother Pharmacol* 1986, **18**, 117–123.

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# Phase I/II Study of Intraperitoneal Iproplatin in Patients with Minimal Residual Disease following Platinum-based Systemic Therapy for Epithelial Ovarian Carcinoma

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**13 patients with minimal residual disease following platinum-based systemic therapy for epithelial ovarian cancer were treated with intraperitoneal iproplatin. A total of three cycles were given at monthly intervals. All patients had minimal residual disease (defined as < 2 cm in diameter) or positive cytology documented at second look laparotomy following systemic chemotherapy. Iproplatin was administered via a temporary dialysis catheter ($n$ = 11) or a semi permanent Tenckhoff peritoneal dialysis catheter ($n$ = 2). The dose of iproplatin ranged from 150 to 450 mg/m$^2$. No responses to therapy were documented. In this trial the major toxic side effects of iproplatin were thrombocytopenia, diarrhoea, nausea and vomiting. The maximum tolerated dose was 300 mg/m$^2$.**
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## INTRODUCTION

DESPITE SIGNIFICANT progress over the last 10 years in the management of advanced epithelial ovarian cancer, the majority of patients continue to die from their disease [1]. Even with optimal initial surgery and appropriate chemotherapy up to 30–50% of women with epithelial ovarian cancer will have residual disease identified at second look surgery [2, 3]. Moreover 30–50% of patients in pathological complete remission following chemotherapy will eventually recur. Patients with pathological complete remissions and minimal residual disease following second look laparotomies have been identified as targets for new therapeutic approaches designed to eliminate any remaining disease [4]. Pharmacological modelling studies have predicted that differences in the peritoneal versus plasma clearance for hydrophilic anti-cancer drugs should result in markedly increased intraperitoneal drug levels compared with the plasma if the drug is administered directly into the peritoneal cavity [5]. Subsequently a number of drugs have been shown to achieve large peritoneal to plasma ratios after intraperitoneal administration [6]. The greatest experience with this approach has been with using cisplatin, the single most active drug in ovarian carcinoma [7, 8]. Some 30% of patients with minimal residual disease following treatment with systemic therapy and subsequently treated with intraperitoneal cisplatin will achieve a complete remission. Its use, however, is associated with a number of severe side effects including nausea, emesis, nephrotoxicity, neurotoxicity and ototoxicity [9]. Attempts have been made to minimise these side effects by synthesising new analogues with improved therapeutic ratios. Iproplatin has been assessed in a number of studies and has been shown to have a similar activity but less toxicity than cisplatin in patients with epithelial ovarian cancer [9–11].

We conducted a phase I/II study to determine the maximum tolerated dose of iproplatin given intraperitoneally to assess local and systemic toxicity and to assess any response to therapy.

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## PATIENTS AND METHODS

*Patients and intraperitoneal administration*

13 patients with histologically confirmed ovarian carcinoma were eligible for this study. All patients had been previously

*Table 1. Patients' characteristics*

| | |
|---|---|
| No. of patients | 13 |
| Age (median) in years | 51 |
| Range | 36–58 |
| Prior chemotherapy | |
| Carboplatin (300 mg/m²) plus cyclophosphamide (600 mg/m²) × three cycles alternating with ifosfamide (5 G/m²) plus doxorubicin (50 mg/m²) × three cycles | 12 |
| Carboplatin (300 mg/m²) plus cyclophosphamide (600 mg/m²) × six cycles | 1 |
| Residual disease found at 2nd look laparotomy: | |
| < 2 cm | 11 |
| > 2 cm | 0 |
| Positive cytology only | 2 |

treated with systemic platinum-based combination chemotherapy (Table 1). Patients assessed clinically and radiologically as being in complete remission or who were felt to have resectable disease after completion of this therapy underwent second look laparotomy/laparoscopy. In 2 patients positive cytology only was found at the second look procedure. The remaining 11 all had evaluable disease of less than 2 cm tumour diameter. All 13 patients had achieved good partial responses following initial chemotherapy and gave informed consent to be included in the study. Ethical committee approval for the study was obtained. All patients had initial creatinine clearances, white blood cell counts and platelet counts greater than 50 ml/min, 3500 × $10^6$/l and 150 × $10^9$/l, respectively.

*Treatment*

Tenckhoff dialysis catheters were placed in the peritoneal cavity of 2 patients at second look laparotomy. Temporary dialysis catheters were inserted under local anaesthetic for the treatment cycles in the other 11 patients. Treatment began 4 weeks after second look surgery. Before delivery of the platinum analogue 30 ml of Omnapaque 110 contrast medium dissolved in 500 ml normal saline and warmed to body temperature was instilled into the peritoneal cavity and the distribution of dye was assessed using computed tomography (CT). In all cases distribution was satisfactory. The contrast medium was drained from the abdomen prior to treatment.

Patients were treated with iproplatin (Bristol-Myers, UK) given intraperitoneally in 2 l of prewarmed normal saline. The 2 l volume was given over 30 min and was left to dwell in the peritoneum for 4 hours and then drained. The starting dose of iproplatin was 150 mg/m². 3 patients were entered at this dose level and in the absence of grade 3 WHO haematological toxicity or evidence of deteriorating renal function subsequent groups of 3 patients were to be entered at 200, 300 and 450 mg/m². 3 patients were entered at each dose level until the maximum tolerated dose defined as WHO grade 4 or prolonged grade 3 toxicity was attained. Treatment was given four times a week. Drug administration was postponed by 1 week if there was not full haematological recovery [white blood cells (WBC) > 3 × $10^6$/l platelets > 100 × $10^9$] from the prior course at scheduled retreatment. Dosage adjustments were made according to the lowest value of WBC and/or platelets measured weekly in the previous course (WBC < 1.0 × $10^6$/l or platelets < 50 × $10^9$/l 25% dosage reduction). Dosages were also reduced according to the creatinine clearance (CrCl) at the time of treatment (CrCl 30–49 ml/min 25% reduction. If CrCl was < 30 ml/min treatment was delayed for 2 weeks and clearance repeated, if < 30 ml/min on the second occasion the patient was withdrawn from the study). A maximum of three cycles were given before reassessment with CT and where appropriate a third look laparotomy/laparoscopy. Treatment was stopped if progression of disease was documented. All patients were given prophylactic high dose maxolon prior to chemotherapy as an anti-emetic and codeine phosphate at a dose of 30 mg intravenously 6 hourly to prevent diarrhoea.

*Table 2. Haematological toxicity*

| Dose (mg/m²) | Patients (*n*) | No of cycles | Nadir WBC (× $10^9$/l) | Nadir platelets (× $10^9$/l) |
|---|---|---|---|---|
| 150 | 3 | 9 | 3.7 (2.9–5.6) | 256 (104–324) |
| 250 | 4 | 10 | 4.0 (2.1–6.1) | 228 (111–418) |
| 300 | 6 | 12 | 3.7 (2.7–12) | 105 (10–249) |
| 450 | 4 | 4 | 3.7 (2.4–4.1) | 33 (12–322) |

Median (range).

*Patient assessment*

Baseline measurements of peritoneal cytology and bacteriology were taken via the access systems prior to treatment by instilling 500 ml of prewarmed saline into the peritoneal cavity. This was left for a dwell time of 15 min and then drained completely and samples taken for bacteriological and cytological examination. This procedure was repeated prior to each treatment cycle. Patients were assessed clinically for disease progression at 2 week intervals. Reponse to treatment was assessed clinically and by computed tomography 2 weeks after the final treatment and where appropriate by third look laparotomy/laparoscopy.

## RESULTS

13 patients received a total of 35 cycles of intraperitoneal iproplatin at doses ranging from 150 to 450 mg/m². The temporary peritoneal dialysis catheters and Tenckhoffs were well tolerated. There were no serious complications on insertion of the catheters or episodes of bacterial peritonitis. There was one episode of inflow obstruction with a Tenckhoff catheter and one of difficulty with outflow with a temporary catheter. In all patients pretreatment intraperitoneal distribution scans demonstrated good distribution of fluid throughout the peritoneal cavity. The dose limiting toxicities of intraperitoneal iproplatin were myelosuppression and diarrhoea which occurred at 450 mg/m². Haematological toxicity is detailed in Table 2.

*Table 3. Non-haematological toxicity*

| Dose (mg/m²) | Patients (*n*) | No. of patients with diarrhoea WHO grade 3/4 | No. of patient with nausea plus vomiting WHO grade 3/4 |
|---|---|---|---|
| 150 | 3 | — | — |
| 250 | 4 | — | — |
| 300 | 6 | 2 | — |
| 450 | 4 | 4 | 2 |

Myelotoxicity was not evident until 450 mg/m$^2$ of iproplatin were used, when 2 of 4 patients had WHO grade 3/4 thrombocytopenia.

Nausea and vomiting were mild (WHO $\leq$ 2) up to 45 mg/m$^2$ when 2/4 patients had prolonged grade 3 (WHO) toxicity. Diarrhoea was a problem (WHO grade 3) in all 4 patients treated at a dose of 450 mg/m$^2$. There were no episodes of clinical chemical peritonitis. Renal failure was not encountered during the study.

*Response data*

Of the 13 patients treated, 5 underwent third look laparotomy at which 3 had static disease and 2 progressive disease. 5 were assessed by CT at which 3 had progressive lesions and 2 had well defined static lesions and it was not felt appropriate to submit these patients to a further laparotomy. 2 patients with positive cytology only at second look operation had positive cytology throughout treatment and did not have a third look procedure. 1 patient refused any further treatment or follow up after one cycle of treatment at 450 mg/m$^2$ due to the severity of her diarrhoea and nausea. The median progression-free interval for all 13 patients was 5 months.

## DISCUSSION

Nearly all the agents with known activity in ovarian cancer have now been examined in intraperitoneal phase I studies [12–15]. These studies have confirmed the promise of pharmacokinetic modelling experiments, with intraperitoneal drug levels 10–1000-fold higher than plasma levels being generated. Iproplatin was introduced into clinical use as a less toxic alternative to cisplatin [11].

Pharmacokinetic data for intraperitoneal iproplatin has previously been described in 5 patients receiving doses between 150 and 300 mg/m$^2$. The authors reported ratios for peritoneal to plasma area under the curves (AUC) ranging from 9.1 to 31.5 and peak peritoneal plasma ratios ranging from 21.1 to 36.4 [16]. A similar large therapeutic advantage for intraperitoneal iproplatin was reported using platinum 195M labelling [17]. The median peak peritoneal to plasma concentration ratio was 24.14 (2.85–55.73), with a median peritoneal to plasma AUCs of 12.57 (2.53–31.57). However, despite a promising pharmacokinetic profile, results of our present study indicate that intraperitoneal iproplatin was not well tolerated at a dose of 450 mg/m$^2$. Diarrhoea, nausea and myelosuppression were significant forms of systemic toxicity at this dose. Of the 4 patients treated at 450 mg/m$^2$ three required dose reductions to 300 mg/m$^2$ for further treatment and one refused any further treatment due to the severity of her diarrhoea and nausea.

In contrast with the promising pharmacokinetic behaviour of intraperitoneal iproplatin the response data were disappointing in patients previously treated with chemotherapy, including a platinum derivative, with no responses and 5/13 patients progressing on treatment. Unfortunately only 13 patients could be entered on this study due to difficulties with the supply of iproplatin, however with no responses in the 10 patients who received a dose within 20% of the maximum tolerated dose we are 95% confident that the true response rate is less than 26%. Although an advantage can be shown for intraperitoneal administration in terms of peritoneal to plasma AUC ratios it is possible that this cannot be translated into an advantage at the site of tumour nodules. It is known that the penetration of cisplatin and carboplatin into tumour nodules is limited to millimetres [18]. To our knowledge similar information on penetration of iproplatin is not yet available. This limitation of the pharmacokinetic advantage of drugs at the cellular level may limit the clinical application of intraperitoneal therapy to all but the smallest of lesions or perhaps those who have responded well to initial therapy and are at risk of relapse from an apparent pathological complete remission.

Based on the outcome of this study it would appear that the suggested dose for future therapy with intraperitoneal iproplatin is 300 mg/m$^2$ to be given every 4 weeks.


1. Gurney H, Crowther D, Anderson H, *et al.* Five year follow up and dose delivery analysis of cisplatin, iproplatin or carboplatin in combination with cyclophosphamide in advanced ovarian cancer. *Annals of Oncol* 1990, **1**, 427–433.
2. Oxols RF, Young RC. Chemotherapy of ovarian cancer. *Semin Oncol* 1984, **11**, 251–263.
3. Schwartz PE and Smith JP. Second look laparotomies in ovarian cancer. *Am J Obstet Gynaecol* 1980, **138**, 1124–1130.
4. Howell S, Zims S, Markman M, *et al.* Long term survival of advanced refractory ovarian carcinoma patients with small volume residual disease treated with intraperitoneal chemotherapy. *J Clin Oncol* 1987, **5**, 1607–1612.
5. Dedrick RL, Myers CE, Bungay PM, Devita VT. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1977, **62**, 1–11.
6. Howell SB. Novel aspects of drug delivery: How to get more drug to the tumour. *Proc ASCO* San Francisco, 1989.
7. Markman M. Intraperitoneal antineoplastic agents for tumours principally confined to the peritoneal cavity. *Cancer Treat Rev* 1986, **13**, 219–246.
8. Bokkel Huinink WW, Dubbleman R, Aasrsten E, Franklin H, McView JG. Experimental and clinical results with intraperitoneal cisplatin. *Semin Oncol* 1985, **12**, 43–46.
9. Anderson H, Wagstaff J, Crowther D, *et al.* Comparative toxicity of Cisplatin, carboplatin (CBDCA) and Iproplatin (CHIP) in combination with cyclophosphamide in patients with advanced epithelial ovarian cancer. *Eur J Cancer Clinc Oncol* 1988, **24**, 1471–1479.
10. Creaven PJ, Madejewicz S, Pendyala L, *et al.* Phase I clinical trial of cis-dichloro-trans-dehydroxy-bis-isopropylamine platinum (IV) (CHIP). *Cancer Treat Rep* 1983, **67**, 795–800.
11. Bramwell VHC, Crowther D, O'Malley S, *et al.* Activity of JM9 in advanced ovarian cancer. A phase I/II trial. *Cancer Treat Rep* 1985, **69**, 409–416.
12. Ozols RF, Young RC, Speyer JL, *et al.* Phase I and pharmacological study of adriamycin administered intraperitoneally to patients with ovarian cancer. *Cancer Res* 1982, **42**, 4265.
13. Howells SB, Chu BCF, Wang W, *et al.* Long duration intracavity infusion of methotrexate with systemic leucovorin protection in patients with malignant effusions. *J Clin Invest* 1981, **67**, 1167.
14. King ME, Howell SB. Intraperitoneal cytarabine therapy in ovarian carcinoma. *J Clin Oncol* 1984, **2**, 662.
15. Howell SB, Pfeifle CE, Wang WE, *et al.* Intraperitoneal cisplatin with systemic thiosulfate protection. *Ann Intern Med* 1982, **97**, 845.
16. Kerr DJ, Harding M, Farmer JG, *et al.* Pharmacokinetics of cis-dichloro-trans-dihydroxy-bis-isopropylamine platinum IV (iproplatin CHIP) in patients with normal and impaired renal function and following intraperitoneal administration. *Med Oncol and Tumour Pharmacother* 1988, **5**, 153–158.
17. Lind MJ, Murphy DJ, Sharma H, *et al.* Comparative intraperitoneal pharmacokinetics of three platinum analogues. *Cancer Chemo Pharmacol* 1991, **28**, 315–317.
18. Los G, McVie JG. Experimental and clinical status of intraperitoneal chemotherapy. *Eur J Cancer* 1990, **26**, 755–762.


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