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Phase II Study of Intraperitoneal Cisplatin Plus Systemic Etoposide as Second-line Treatment in Patients With Small Volume Residual Ovarian Cancer

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The efficacy and toxicity of intraperitoneal (i.p.) cisplatin plus systemic etoposide were studied in 36 patients with small (<2 cm) residual i.p. ovarian cancer after achieving a partial response to platinum-based, first-line chemotherapy. Treatment comprised 90 mg/m² i.p. cisplatin with intravenous (i.v.) sodium thiosulphate (day 1) and 600–800 mg/m² i.v. etoposide (days 1 and 2), every 4 weeks for four to six cycles. 7 patients achieved a pathological complete response (pCR), one a pathological partial response and 16 were clinically stable without evidence of disease. After a median follow-up of 13 months, the median progression-free survival (PFS) was 11 months (95% confidence interval 7–16 months). The actuarial PFS at 24 months is 22% (95% confidence interval 8–36%). Three of six relapses after achieving a pCR (50%) were sited i.p., and 9 of 14 other patients with disease progression (64%) had an i.p. relapse, indicating insufficient local efficacy. There was no renal toxicity, but grade 3–4 leucopenia occurred in 63% and grade 3–4 thrombocytopenia in 8% of cycles, while nausea, vomiting and complete alopecia were common. Although side-effects were acceptable, the efficacy of treatment with i.p. cisplatin plus i.v. etoposide is limited.

Key words: intraperitoneal chemotherapy, etoposide, cisplatin, ovarian cancer
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INTRODUCTION

MOST PATIENTS with ovarian cancer will have advanced disease (FIGO stages III–IV) at initial presentation and long-term efficacy of chemotherapy in these patients is often disappointing. Although a majority of patients will respond to first-line platinum-based chemotherapy, residual disease at second-look laparotomy is still found in a substantial number of patients and pathological complete response (pCR) is achieved in only 25–30% [1]. Intraperitoneal (i.p.) "salvage" chemotherapy is a valuable option in patients with small residual disease, as it has been reported to result in pCR in 30% of cases [2–4], and several studies have shown that patients with an initial partial response to intravenous (i.v.) platinum-based, first-line, systemic therapy are still sensitive to i.p. cisplatin [5, 6]. Intraperitoneal chemotherapy offers the pharmacological advantage of a high concentration area-under-the-curve ratio in the peritoneal cavity compared to plasma and a possibility for dose escalation, especially when cisplatin is used in conjunction with i.v. sodium thiosulphate, which prevents renal toxicity [7, 8]. However, there is doubt regarding the efficacy of i.p. therapy alone because of limited local penetration and eventual metastases outside the peritoneal cavity [9, 10].

Because etoposide has shown synergistic activity with cisplatin *in vitro* [11, 12] and is an active drug for second-line treatment in patients with platinum-resistant disease [13], we chose to investigate a regimen combining i.p. cisplatin with systemic etoposide. Etoposide was given i.v., divided over 2 days to enhance activity without inducing undue burden to the patient.

In a previously published dose escalation study [14] we have shown that the combination of 90 mg/m² i.p. cisplatin and 600 mg/m² i.v. etoposide was feasible, with higher doses of etoposide precluded by the occurrence of a generalised skin rash. The study period was extended to determine progression-free survival, and we now report the data from 36 ovarian cancer patients with small residual disease after a partial response to platinum-based first-line chemotherapy.

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PATIENTS AND METHODS

Eligibility requirements were FIGO (International Federation of Gynaecology and Obstetrics) stage III or IV epithelial ovarian cancer, partial response (PR) to standard induction treatment with a platinum-based regimen and residual i.p. disease, largest diameter less than 2 cm after second-look laparotomy.

Other inclusion criteria were WHO performance status ≤2, age ≤75 years, life expectancy ≥3 months, creatinine clearance ≥60 ml/min, white blood cell count $\geq 3.0 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l. The protocol was approved by the local medical ethical committee and informed consent was obtained from all patients.

Consecutive patients treated from December 1988 to April 1993 were included in this analysis. All patients had a Port-A-Cath peritoneal catheter (Pharmacia, Woerden, The Netherlands) placed at the time of restaging laparotomy. Proof of adequate i.p. fluid distribution, as shown by the diffusion pattern of 75 MBq ^{99m}TC-colloid in 21 of normal saline, was required. Patients with inadequate distribution were excluded and received other treatments. Treatment was started as soon as possible after restaging and consisted of i.p. cisplatin 90 mg/m^2 in 2 l of normal saline over 2 h on day 1, and i.v. etoposide 600 mg/m^2 divided into two doses, each given in 1 l of normal saline over 1 h, on days 1 and 2. Patients receiving 800 mg/m^2 etoposide as part of the feasibility study were also included. While receiving cisplatin, 3 g/m^2 i.v. sodium thiosulphate in 1 l of dextrose/saline was given over 2 h followed by 12 g/m^2 i.v. sodium thiosulphate in 1 l of dextrose/saline over the next 6 h. Cycles were repeated every 4 weeks for a total of 6 weeks, unless progression occurred earlier. Patients with only microscopic disease were allowed four cycles. Premedication consisted of 20 mg slow-release morphine (MS-Contin, Dagra-Pharma, Diemen, The Netherlands) orally and 10 mg diazepam as a microenema. The anti-emetic regimen comprised 12 mg dexamethasone i.v. bolus, 25 mg chlorpromazine over 6 h i.v. and 20 mg metoclopramide i.v. every 6 h. From April 1992 onwards, 5-HT$_3$ receptor antagonists were routinely used. For evaluation of toxicity, standard WHO criteria were applied. Blood counts, serum electrolytes and renal function were determined before every cycle and nadir blood counts were checked on day 15. Additionally, at every treatment cycle serum CA-125 levels were determined and, if possible, peritoneal washings for cytology were collected through the access port. After completion of treatment, disease assessment, including vaginal examination and vaginal ultrasound, was performed. Patients with a clinical CR (cCR) were proposed for restaging laparotomy.

At restaging laparotomy, biopsies were taken from multiple (at least eight) different sites including the upper and lower paracolic gutters on both sides, bilateral diaphragm and cul-de-sac. Routinely washings were done from the whole peritoneal cavity. Follow-up consisted of physical examination every 3 months with serum CA-125 measurement and gynaecological examination, including vaginal ultrasound every 6 months. Serum CA-125 levels were measured using an automated microparticle enzyme immunoassay (IMx CA 125, Abbott Diagnostics, Chicago, Illinois, U.S.A.). Before 1991, an enzyme-linked immunosorbent assay (Abbot Diagnostics) was used. The upper limit of normal is 35 kU/l, being the 97.5 percentile in healthy female blood donors. In postmenopausal women or after hysterectomy, the upper limit of normal is 30 kU/l.

Treatment responses were defined as follows: cCR is the absence of any signs of disease at assessment according to protocol and normal CA-125. pCR is the absence of disease at surgical evaluation, including multiple random biopsies and peritoneal washings. PR is >50% decrease of all measurable lesions. Pathological PR (pPR) is a partial remission at surgical evaluation including pathological examination of resected or biopsied material. The following conditions were considered progressive disease (PD) or relapse: ≥25% increase of measurable residual lesions, recurrence at previous sites of disease or appearance of any new lesion, clinical deterioration in absence of any other causative condition than malignant disease and biochemical progression. Biochemical progression is defined as an increase in tumour marker level above normal if ≥100% increase on two consecutive measurements is found. The measurement which marks the onset of rising CA-125 levels is considered to be the time-point of progression in cases were there is no other proof of progressive disease. Stable disease (SD) is defined as no change, or changes insufficient to meet criteria for PR or PD.

Statistics

Confidence intervals (CI) for response rates and survival were calculated using standard techniques. Probability of survival was calculated by the Kaplan–Meier method. The χ^2 test was used for comparison of proportions and Gehan's test was used for difference in median survival. P values <0.05 were considered statistically significant.

RESULTS

36 patients with residual disease <2 cm were entered in the study. 20 of these were included in an earlier report [14]. Only 2 patients were excluded from this study because of inadequate intraperitoneal fluid distribution. Disease characteristics of the patients are summarised in Table 1. At diagnosis, 5 patients were stage IV, because of pleural effusions in three and liver metastases in two, with complete resolution of these extraperitoneal lesions at the time of second-look laparotomy. 33 patients

Table 1. *Patients' characteristics*

	Number of patients
Total number	36
Age (years)	
Median	55
Range	22–71
Histology	
Serous	29 (81%)
Endometroid	3 (8%)
Undifferentiated	3 (8%)
Unclassified	1 (3%)
Differentiation grade	
Well differentiated	5 (14%)
Moderate	11 (31%)
Poor	15 (42%)
Unknown	5 (14%)
Initial FIGO stage	
III	31 (86%)
IV	5 (14%)
Residual disease at second look after debulking	
Microscopic	15 (42%)
≤5 mm	11 (31%)
6–10 mm	7 (19%)
11–19 mm	3 (8%)

received carboplatin and cyclophosphamide as first-line treatment and 3 patients cisplatin and cyclophosphamide. The median time between second-look laparotomy and start of the experimental treatment was 5 weeks (range 2–9). 28 patients were scheduled for 600 mg/m^2 etoposide and 8 patients were scheduled for 800 mg/m^2 etoposide as part of the feasibility study [14]. Of 28 patients scheduled to receive 600 mg/m^2 etoposide, 17 received six cycles, 4 patients with microscopic disease received four cycles and treatment was discontinued because of PD in 7 patients after two to four cycles. Of the 8 patients scheduled for 800 mg/m^2, 7 received six cycles, with etoposide dose reduced in 2 patients, and 1 patient was withdrawn for PD after four cycles. A total of 186 cycles were given and the numbers with dose modified were as follows: i.p. cisplatin was reduced in 11 cycles (6%), i.v. cisplatin was substituted for i.p. in three cycles (2%) because of catheter problems, etoposide was reduced in 17 cycles (9%) and etoposide was omitted in six cycles (3%). Of all cycles, 159/186 (85%) were given at full dose, where an etoposide dose of at least 600 mg/m^2 is considered optimal treatment.

Response to therapy and progression-free survival

Responses for all 36 evaluable patients, receiving either 600 or 800 mg/m^2 etoposide, are shown in Table 2. Of the 9 patients who had surgical restaging, 7 had a CR, 1 a pPR and 1 PD. Response was evaluated clinically in the other 27 patients: 15 patients had a cCR, 4 were considered stable because of unchanged elevated CA-125 levels in the absence of clinical tumour activity, and 9 patients had PD disease. The total number of patients responding was 23 (64%; 95% CI 48–80%).

The median duration of follow-up was 13 months (range 7–50). Progression-free survival (PFS) is shown in Figure 1. The median time to progression was 11 months (95% CI 7–16 months). In patients with pCR, median time to progression was 12 months, and in patients with a cCR median time to progression was 23 months. 7 patients (1 pCR and 6 cCR) still have no evidence of disease at 10, 10, 13, 21, 25, 33 and 34 months of follow-up. The sites of progression in 9 patients with PD were i.p. disease in 6 patients, 1 patient had an abdominal wall metastasis, 1 patient developed supraclavicular lymph node metastases and 1 a malignant pleural effusion. Of the 6 patients relapsing after pCR, 3 had i.p. sites of disease, 1 had liver metastases, 1 an umbilical metastasis, and 1 a subcutaneous metastasis. Of the other 14 patients with relapsing disease, 9 showed i.p. progression, 1 had liver metastases, 1 brain metastases and 3 had biochemical progression as the only sign of relapse. Overall, 18 of 36 patients (50%) had an intraperitoneal relapse and thus were considered local treatment failures. 2 patients with a proven relapse had persistently normal CA-125 values.

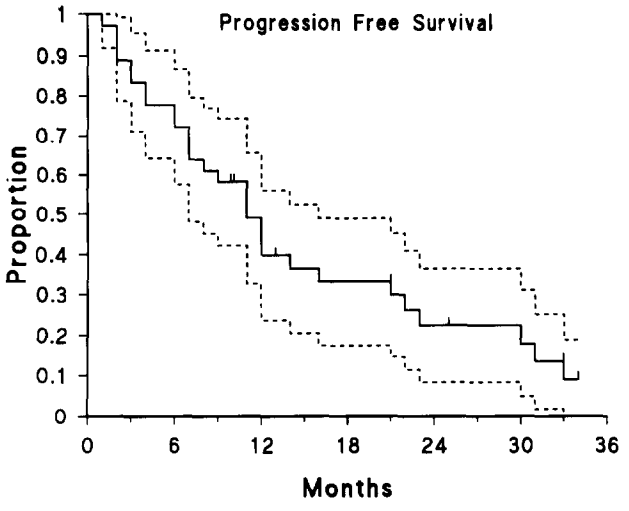

Figure 1. Progression-free survival for all evaluable patients. Broken lines indicate 95% confidence limits.

13 out of 15 patients (87%) with microscopic disease after initial therapy developed a cCR, compared with 10 of 21 patients (48%) with macroscopic disease (P = 0.04). The influence of the diameter of residual disease on PFS is shown in Figure 2. The median PFS in patients with microscopic disease was 14 months (95% CI 11–30 months), compared to 8 months (95% CI 4–16 months) in patients with macroscopic disease (P = 0.04).

CA-125 levels were elevated in 22/36 (61%) of patients. Table

Table 2. Response to treatment related to residual tumour volume after second-look laparotomy following primary treatment

	pCR	cCR	pPR	SD	PD	Total
Surgical evaluation (n = 9)						
Microscopic	4	—	—	—	—	4
≤5 mm	—	—	1	—	—	1
6–10 mm	2	—	—	—	1	3
11–19 mm	1	—	—	—	—	1
Clinical and biochemical evaluation (n = 27)						
Microscopic	—	9	—	1*	1	11
≤5 mm	—	6	—	3*	1	10
6–10 mm	—	—	—	—	4	4
11–19 mm	—	—	—	—	2	2
Total	7 (19%)	15 (42%)	1 (3%)	4 (11%)	9 (25%)	36

pCR, pathological complete response; cCR, clinical complete response; pPR, pathological partial response; SD, stable disease; PD, progressive disease. *No change in elevated CA-125 during therapy, in the absence of measurable disease.

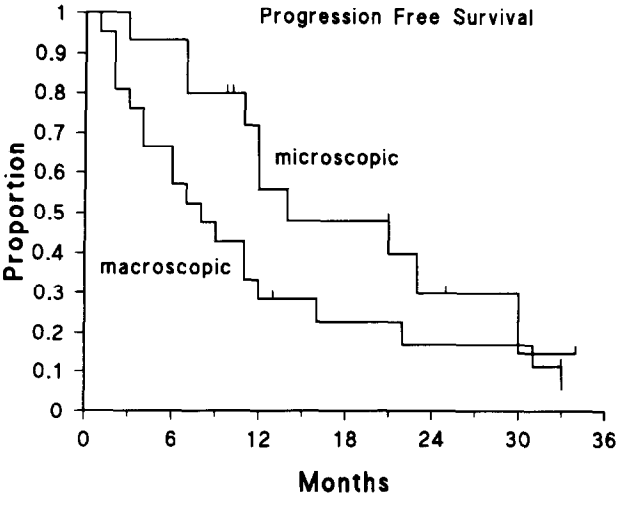

Figure 2. Progression-free survival comparing patients with microscopic (n = 15) and macroscopic (n = 21) residual disease at second-look laparotomy.

Table 3. Relationship between post-treatment CA-125 levels at the end of therapy and tumour response

	pCR	cCR	pPR	SD	PD	Total
Remained normal	3	11	—	—	—	14 (39%)
Normalised	4	4	1	—	3	12 (33%)
Remained elevated	—	—	—	4	6	10 (28%)

See Table 2 for abbreviations.

3 shows the results for CA-125 related to response. At the end of study treatment, CA-125 was normal in 24 patients and normalised during follow-up in 2 patients with a pCR.

Toxicity and complications of treatment

Toxicity for 800 mg/m^2 etoposide was described in detail in our previous report [14]. Treatment at this dose produced a toxic skin rash and 600 mg/m^2 was, therefore, considered to be the maximum tolerated dose.

Toxicity of 600 mg/m^2 i.v. etoposide plus 90 mg/m^2 i.p. cisplatin was analysed in the 28 patients scheduled for this dose. Haematological toxicity is shown in Table 4. Nadir values were available for 54 of 134 (40%) cycles administered. Grade 3–4 leucopenia developed in 63% and grade 3–4 thrombocytopenia in only 8% of cycles. Leucopenic fever occurred in only 4% of cycles. Anaemia grade 1 developed in 47% of patients, grade 2 in 25%. Complete alopecia and nausea and vomiting grade 2–3, despite the use of anti-emetics, were common in all patients. Neurotoxicity or more than grade 1 nephrotoxicity were not seen. Toxic skin rashes occurred in 3 patients as a reaction to etoposide, and etoposide had to be discontinued thereafter in 1 patient. In 1 patient a skin rash was caused by cisplatin, as skin tests with intracutaneous cisplatin were positive. Intraperitoneal catheter obstructions occurred in 2 patients, and in 1 of these i.v. cisplatin was substituted for i.p. cisplatin. In a third patient, one cycle was delayed because of catheter leakage but further cycles were uncomplicated.

DISCUSSION

In this study, we confirmed that a regimen consisting of i.p. cisplatin, combined with i.v. sodium thiosulphate and systemic etoposide every 4 weeks is feasible. There was no renal toxicity above grade 1 and haematological toxicity seldom led to leucopenic fever. Complications related to i.p. cisplatin administration and catheter leakage or obstruction were infrequent, in contrast to some other studies [15, 16]. However, one should be aware of a risk of allergic reactions to etoposide, as reported by other investigators [17]. Grade 2–3 nausea and vomiting were common side-effects and particularly troublesome. Some improvement was possible with the new 5-HT$_3$ receptor antagonists. Alopecia occurred in all patients. The large volumes administered to the intraperitoneal cavity never gave symptoms of fluid overload.

Table 4. WHO grade of haematological toxicity as percentage of cycles

	WHO grade				
	0	1	2	3	4
Leucopenia	11%	2%	24%	53%	10%
Thrombocytopenia	68%	6%	18%	6%	2%

The results show that a substantial number of patients (64%) had a clinical response to this regimen. Only a minority of our patients had surgical restaging, but in a comparable group of patients, 60% of patients with a clinical response were found to have a pCR [18].

Without surgical restaging, the actual response could not be measured in the 15 patients considered to have a cCR, because of small tumour volumes and normal CA-125 before treatment. These patients would, therefore, more appropriately be classified as "clinically stable without evidence of disease". Because of these restrictions and the limited value of the negative outcome of second-look laparotomy [19], the PFS is a more reliable way to evaluate treatment efficacy.

A considerable number of phase II studies investigating the role of various i.p. chemotherapy regimens has been published, but many of these lack more mature survival data. In our study, we show that, despite the high response rate, the predicted PFS (Figure 1) is still limited with a median of 11 months and a 2-year PFS of 22%. It is difficult to compare these results with other published studies because of differences in patients' characteristics. Most studies include both patients with residual disease and patients with relapse, although it is shown that these have different response rates for cisplatin-based i.p. chemotherapy [20]. Other confounding factors are the type of, and response to, first-line treatment. In three studies reporting survival data in patients with residual or relapsed small volume disease using platinum-based i.p. chemotherapy, the median PFS were 11, 13.7 and 14 months [5, 21, 22]. These values can be compared with the 15 months median PFS after second-look laparotomy in 116 patients with persistent or recurrent disease after first-line chemotherapy (≤5 mm in 76%) treated in the Mayo Clinics between 1977 and 1986 with a variety of other second-line modalities [23].

Several studies have shown the residual tumour volume to be a prognostic factor for response to i.p. chemotherapy [18, 19, 23, 24]. We also found a 40% higher clinical response rate and a longer median PFS in patients with microscopic disease. The difference in PFS may be caused by earlier manifestations of progression in patients with macroscopic disease, and only large randomised studies stratified for tumour volume can solve this issue.

Our experience shows that many patients (50%) had an i.p. relapse, and thus can be considered local treatment failures. This was also the case in patients with a surgical defined CR. There are several possibilities for improvement. The cisplatin dose can be further increased to 200 mg/m^2 as renal toxicity can be prevented by sodium thiosulphate [7, 8, 21]. The new drug Taxol is under investigation for i.p. administration [25], and drug targeting using liposomes may enable more prolonged exposure to local high drug concentrations. In animal experiments, liposomes have been successfully directed to human ovarian cancer xenografts using tumour-specific antibodies bound to their surface [26].

The optimal agents (and schedule) for systemic treatment in conjunction with i.p. cisplatin should also be further investigated. Efficacy of etoposide is schedule dependent and clinical studies have indicated an advantage for protracted low-dose administration [27].

Recently, the efficacy of low-dose oral etoposide was shown in patients with refractory ovarian cancer [28, 29].

Furthermore, subset analysis of clinical studies should help

identify patients who are particularly sensitive to i.p. chemotherapy.

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