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A Phase I–II Study with Intraperitoneal Cisplatin plus Systemic Etoposide in Patients with Minimal Residual Ovarian Cancer

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In patients with residual ovarian cancer after standard platinum-based induction, dose intensification was achieved by intraperitoneal administration of cisplatin 90 mg/m² with intravenous Na thiosulphate and increasing dosages of etoposide. 40 patients entered the study, 4 on 200 mg/m², 6 on 400 mg/m², 22 on 600 mg/m² and 8 on 800 mg/m² etoposide. The optimal dose for etoposide was 600 mg/m². 29 patients on the two highest dose steps were evaluable for response. 14 patients reached a complete remission, which was surgically confirmed in 6. All these patients initially had tumour residuals smaller than 1 cm. 3 patients had a partial response, 4 had stable disease and 8 progressed. At a maximal follow-up of 2 years (median 12 months), median time to progression was 12 months and median overall survival was 14 months. Of the 14 patients with complete remission, 2 relapsed at 9 and 11 months. Apart from a rash, in 4 of 22 patients at 600 mg/m² and in 5 of 8 at 800 mg/m² etoposide, the main toxicity was leukopenia grade 3–4 in 58% of cycles on 600 and in 76% at 800 mg/m² etoposide. Leukopenic fever, however, occurred only three times; thrombocytopenia was rare. Cycles had to be delayed sporadically and the etoposide dose was reduced in 9% of all cycles at 600 and in 11% at 800 mg/m². Intraperitoneal instillation of cisplatin gave no peritoneal symptoms. Intraperitoneal cisplatin with intravenous etoposide was tolerable and effective for patients with small tumour residuals after induction for stage III ovarian cancer.
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INTRODUCTION

PLATINUM-BASED combination chemotherapy is the most effective treatment for disseminated ovarian cancer [1]. As a complete remission is reached only in a minority of patients, additional treatment is often indicated. The intraperitoneal administration of cisplatin has proved to be effective in patients with small tumour residuals [2–4], while deterioration of renal function can be prevented by the simultaneous systemic administration of Na-thiosulphate [2, 3]. Etoposide is one of the few effective drugs in second line treatment [5] and may be synergistic with cisplatin [6]. By virtue of the modest myelotoxicity of cisplatin, combination with etoposide is feasible, but its intraperitoneal use is limited by chemical peritonitis [3]. Therefore, we performed a feasibility and phase II study with a fixed dose of cisplatin intraperitoneally together with a stepwise increase of intravenous etoposide.

PATIENTS AND METHODS

Patients with stage III ovarian cancer with a residual tumour of less than 2 cm diameter after standard induction treatment with a platinum-based combination, were eligible for study, provided they had not progressed during primary treatment, creatinine clearance was above 60 ml/min and bone marrow function was sufficient. A permanent peritoneal access port (PAP) (Port-A-Cath) was placed. Before treatment, patients received 20 mg slow release morphine (MS-Contin) orally and 10 mg diazepam as a microenema. Anti-emetic regimen comprised 12 mg dexamethasone intravenous bolus, 25 mg chlorpromazine over 6 h intravenously and 20 mg metoclopramide suppositories every 6 h. Diuresis and blood pressure were monitored closely in all patients. Before treatment, which was started 2–4 weeks after laparotomy, the fluid distribution was checked by instillation of 75 MBq ^{99m}Tc-colloid in 2000 ml normal saline. The next day, 1000 ml saline at 37°C was given over in 2 h intraperitoneally and cisplatin 90 mg/m² dissolved in 1000 ml saline at 37°C was instilled intraperitoneally over 4 h. While receiving cisplatin, 1000 ml dextrose/saline containing 3 g/m² Na-thiosulphate was given in 2 h intravenously, followed by 12 g/m² Na-thiosulphate in 1000 ml dextrose/saline over the next 6 h, followed by 1000 ml dextrose/saline in the next 6 h. Half the amount of etoposide was given intravenously in 1000 ml saline in 1 h before cisplatin administration, and the other half was given 18 h later on day 2.

The dose of etoposide was escalated from 200 mg/m² (4 patients), 400 mg/m² (6 patients), 600 mg/m² (22 patients) to 800 mg/m² (8 patients). On 800 mg/m² a toxic rash occurred which was considered dose-limiting, and 600 mg/m² was then chosen as the maximally tolerated dose (MTD) for further evaluation. The treatment efficacy was evaluated only in patients receiving 600 or 800 mg/m². Cycles were repeated every 4 weeks for a total of 6 cycles unless progression occurred earlier.

For evaluation of toxicity, standard WHO criteria were applied and scored after every cycle. The evaluation of response was done according to UICC criteria in patients with measurable tumour deposits. Additionally, at every treatment cycle, serum CA-125 level was determined and cytology of peritoneal washings was performed. A 100% increase of marker levels above

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Table 1. Percentage of cycles with WHO grade leukopenia

Dose (mg/m²)	No. of patients	WHO grade (% of cycles) 0	1	2	3	4	No. of cycles
200	4	42	52	6	—	—	21
400	6	8	32	48	11	1	25
600	22	3	3	36	52	6	101
800	8	—	—	24	70	6	46
Total	40						193

Table 2. Relation between residual tumour diameter at laparotomy after induction treatment and treatment outcome

Residual tumour at second look	pCR	CR	PR	SD	PD	Total
microscopic	3	4	1	—	—	8
≤ 1 cm	3	4	1	3	2	13
≥ 1 cm	—	—	1	1	6	8
	6	8	3	4	8	29

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, p = pathologically confirmed.

normal, the appearance of new lesions or an increase of tumour measurements ≥25% were considered as signs of tumour progression. In patients with a clinically complete remission, i.e. a negative vaginal examination, vaginal ultrasound, normalised marker levels and negative washings, a second look laparotomy was proposed in order to have a histopathological confirmation of the clinical results. 6 patients consented to this procedure.

RESULTS

40 patients, aged 34–70 years, median age 56 years, were entered in this study. Of the 40 patients entering this study, 6 had been previously treated with a cisplatin based combination and 34 patients with carboplatin plus cyclophosphamide. 28 were treated immediately after induction therapy, and 12 at relapse or progression a median of 15 months (range 9–36 months) after induction treatment.

Myelotoxicity is represented in Table 1 and mainly comprises dose-dependent leukopenia. 2 patients were readmitted for leukopenic fever. On 600 mg/m² WHO thrombocytopenia grade I was present in 9 (9%) and grade II in 11 (11%) of cycles; on 800 mg/m² grade I in 3 (7%), grade II in 3 (7%), grade III in 2 (4.5%) and grade IV in two cycles (4.5%). Platelet transfusion was given only on one occasion. Leukopenia was dose-dependent ($P < 0.01$) for grade 3–4 leukopenia.

A generalised skin rash was considered to be the dose-limiting side-effect. The rash did not recur on re-exposure. On 600 mg/m² the rash occurred in 4 out of 22 patients, but 5 out of 8 patients on 800 mg/m² etoposide. 1 patient experienced hypotension during etoposide infusion in the fifth cycle and further administration of etoposide was stopped. Another patient with facial flushing and hypotension during the fifth cycle developed positive skin tests against cisplatin. Cisplatin was stopped in this patient.

The incidence of nausea and vomiting did not appear to correlate with the dosage of etoposide and was moderate to severe on the day of cisplatin administration, despite antiemetics. There was no abdominal pain from the intraperitoneal fluid or cisplatin. In 2 patients the intraperitoneal administration of cisplatin became painful due to local adhesions, and both patients received two additional cycles of 75 mg/m² cisplatin intravenously. Lassitude and general malaise lasted for 1–5 days after discharge but disappeared completely between cycles. Diarrhoea did not occur. 1 elderly patient, suffering from severe malaise after the first cycle refused further treatment and could not be evaluated for efficacy.

1 patient, who had grade I neuropathy after previous cisplatin, complained about an increase of paraesthesiae without motor symptoms. Grade I nephrotoxicity occurred in 2 patients, for which cisplatin dosage was reduced to 50%. We did not see any cardiopulmonary problems in spite of the large amount of fluid and solute overload by Na-thiosulphate, which constitutes about 5 meq/g.

Efficacy

10 patients treated with 200 and 400 mg/m² etoposide were not evaluated for treatment effect. Of the 22 patients receiving 600 mg/m² etoposide, 21 are evaluable; 1 patient refused treatment after the first cycle. 8 patients did not complete six cycles due to tumour progression. Responses are shown in Table 2 and are pooled for all patients receiving 600 or 800 mg/m² etoposide. All complete responses were found in patients with tumour residuals smaller than 1 cm, while no patients with larger tumours reached complete remission (CR) and only one partial remission (PR). At a maximal follow-up of 2 years, the median time to progression was 12 months. The median overall survival of all patients was 14 months. Of the 14 patients reaching a clinical CR, 2 relapsed at 9 and 11 months, respectively, and the progression free survival amounts to 77% at 2 years.

DISCUSSION

Cisplatin was given intraperitoneally to patients with a limited amount of residual tumour, creating a high local drug concentration in order to increase response. Tissue penetration by cisplatin given intraperitoneally is better than by other platinum analogues [7]. The tissue concentration of cisplatin is correlated with the intravenous dose and the plasma AUC after intraperitoneal administration is equivalent to intravenous treatment [8]. Moreover, by giving cisplatin dissolved in normal saline, the percentage free platinum will be relatively high, which facilitates tissue binding compared with protein-bound cisplatin in the plasma. In addition, local irritation is no problem, and systemic toxicity can be prevented by suitable antidotes such as Na-thiosulphate (STS). In the circulation this compound will bind to cisplatin and may thus decrease its systemic efficacy to some extent [9]. Carboplatin, on the other hand, is activated less rapidly within the cell and forms DNA-platinum adducts more slowly than cisplatin after tissue exposure *in vivo* [10], while its plasma half life is shorter [11]. Early evacuation of carboplatin may thus result in suboptimal activity [12, 13]. An advantage of carboplatin is its less pronounced nephrotoxicity. The administration of Na-thiosulphate can prevent the nephro- but not the neurotoxicity of systemic cisplatin [2, 3]. In this study, the cisplatin dosage had to be reduced for nephrotoxicity in only 2 patients, which is low compared with renal toxicity after intraperitoneal cisplatin without thiosulphate [9, 14].

Cisplatin was combined with systemic etoposide, which has shown definite activity as a second line agent, and is synergistic with cisplatin *in vitro* and in animal studies [6]. For etoposide

given intraperitoneally, the local effect and pain were dose limiting [3], while its efficacy after systemic use depends a great deal on the dose and schedule given [15]. In view of the etoposide half life of about 6 h [16], we choose to give etoposide with a 18 h interval on two successive days, in order to maintain a blood level over at least 48 h. In this study, a rash and leukopenia proved to be dose-limiting, but mucositis did not occur.

This study provides no answer to the question of cross resistance between cisplatin and carboplatin, because progressive patients were not eligible. The study shows that the combination of cisplatin and etoposide is effective in patients with small tumour residuals. Surprisingly, however, when this combination was given to chemotherapy naive patients, it proved rather disappointing, as the clinical CR in 56% of patients was surgically confirmed only in 3 out of 7 patients [17]. The predictive value of combined normal cytology and marker levels in our study is remarkable, predicting 6 out of 6 patients with pCR. It is suggestive that this kind of local treatment is applicable only in small tumour volumina. This point is confirmed by more recent studies [18, 19].

Allergic reactions to cisplatin occurred only once. The generalised rash after etoposide occurred only after the first exposure. It may be caused by the drug or its solvent and evidently some kind of tolerance will develop [20].

The myelotoxicity of this combination was acceptable. In less than 5% of all cycles the dosage of etoposide had to be reduced for myelotoxicity. In order to increase the efficacy of this combination, one might consider to combine cisplatin with a modulator of drug resistance, e.g. inhibitors of DNA repair. Combining higher dosages of etoposide with carboplatin and autologous bone marrow support with haematopoietic growth factors will be the subject of further studies [21, 22].

The exact value of intraperitoneal treatment has to await comparative studies such as now are being performed in San Diego and by the SWOG [23]. The remission rate reached by intraperitoneal treatment in comparison with second line drugs given intravenously appears to justify this approach.

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