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Carboplatin/etoposide as first-line chemotherapy in advanced ovarian carcinoma: a pilot study

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Summary. In a pilot study, 18 patients with advanced ovarian cancer were evaluated for tolerance and response to a combination treatment with a fixed dose of carboplatin (350 mg/m^2 given i.v. on day 1) and escalated doses of etoposide (70–130 mg/m^2 daily given i.v. on days 1–3) as first-line chemotherapy. The maximum tolerated dose of etoposide was 130 mg/m^2 when given i.v. on days 1–3 in combination with 350 mg/m^2 carboplatin given i.v. every 4 weeks. At these dose levels, bone marrow toxicity was manageable and did not appear to be cumulative. In all, 12 objective responses, including 9 complete responses (CRs) and 3 partial responses (PRs), were achieved in 18 patients; 6 of the 9 CRs were confirmed as pathological CRs by second-look surgery.

Introduction

Combinations of cisplatin and alkylating agents are generally considered for current first-line chemotherapy of advanced ovarian cancer [12, 20]. Prospective randomized studies have shown that the addition of Adriamycin [4, 11] or of Adriamycin + hexamethylmelamine [8, 22] to cisplatin + alkylators does not significantly improve the antitumor activity but induces a higher incidence of toxicity [4, 8, 11, 22]. Irrespective of the number of agents used in these combinations, cisplatin-containing regimens induce remission rates of 50%–85%, including a rate of 30%–60% for a clinically complete response (CR), resulting in a median survival of 19–47 months [4, 8, 11, 12, 17, 20, 22, 24]. Treatment with cisplatin-containing regimens is limited by drug-induced severe nausea, vomiting, nephrotoxicity, peripheral neuropathies and ototoxicity [4, 8, 11, 17, 22, 24].

Carboplatin is a new platinum derivative with antineoplastic activity in epithelial ovarian cancer that is similar to the parent compound [1, 23, 29–31]. Moreover, carboplatin induces statistically significantly less nephro-, oto-, neuro- and gastroenteric toxicity [1, 23, 29–31] than does cisplatin, whereas bone marrow suppression is the dose-limiting toxicity [6, 23, 29]. Analogous to earlier trials with cisplatin, the efficacy of carboplatin in combination chemotherapy has been explored in association with alkylating agents. Three- and four-drug combinations including also Adriamycin [5, 7] and hexamethylmelamine have been evaluated in several studies [26, 27].

When given at adequate doses, etoposide is active in ovarian cancer that is resistant to cisplatin and cyclophosphamide regimens; in these situations, it has induced overall responses in 31% of patients, including a 15% CR rate, resulting in a median response duration of 5–8+ months [14, 18]. Furthermore, etoposide is well tolerated [15], has synergistic activity with carboplatin in experimental tumors [3] and has a different molecular mode of action [2, 16, 25]. Based on these experimental and clinical data, the combination of carboplatin and etoposide seemed to be of interest as first-line chemotherapy in advanced ovarian cancer. Because of the overlapping myelosuppression, we initiated a pilot study to define the dose of etoposide that can safely be given in combination with 350 mg/m^2 carboplatin [14, 26].

Patients and methods

Eligible patients had histologically confirmed epithelial ovarian cancer (FIGO stage III or IV) and had not undergone prior radio- and/or chemotherapy. They were ≤75 years of age and had a performance status of 0–2 according to WHO criteria, a life expectancy of ≥3 months, normal bone marrow function (WBC, ≥4,000/mm^3; platelets, ≥100,000/mm^3), normal renal function (serum creatinine, ≤1.5 mg/100 ml; creatinine clearance, ≥60 ml/min), and normal liver function (serum bilirubin, ≤1.5 mg/100 ml). Informed consent was obtained from all patients.

Pretreatment and follow-up examinations. Before treatment, all patients underwent a full physical examination and the following laboratory determinations: full blood count, serum liver-function tests, serum creatinine, creatinine clearance, serum electrolytes. The stage of disease was assessed by means of chest X-ray, computerized tomography (CT)

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and/or ultrasound of the abdomen, pelvis, and other relevant sites, and i.v. urogram. Bone scintigraphy, mammography, CT of the brain, bone marrow biopsy, cystoscopy, and rectoscopy were performed if clinically indicated.

The treatment plan included a primary laparotomy for definition of the extent of disease and for removal of as much tumor as feasible. The measurable tumor parameters were determined before chemotherapy, before each cycle, 4 weeks after the last cycle, and then every 3 months. The full blood count, serum creatinine levels and creatinine clearance, electrolytes, and liver function were determined prior to therapy, prior to each cycle, and 4 weeks after the last cycle. During treatment, complete blood counts and serum creatinine levels were monitored weekly. Audiometry was done before the first and after the last course of chemotherapy. Surgical restaging was done in patients who showed either no clinically detectable tumor or a potentially resectable mass after the fifth or sixth cycle of treatment.

Treatment response/toxicity. Patients were considered to be evaluable for response and toxicity if they had received at least one cycle of chemotherapy. Tumor response and toxicity were classified according to WHO criteria [28]. Biopsy proof of disease status at second-look laparotomy was required to define pathological CRs and PRs.

Treatment plan. This study was designed as a dose-finding pilot study in which a fixed dose of carboplatin was combined with escalated doses of etoposide. The starting dose for carboplatin was 350 mg/m^2 given i.v. on day 1 and that for etoposide was 70 mg/m^2 given i.v. on days 1–3. The etoposide dose was escalated by 20 mg/m^2/day. Carboplatin was given i.v. in 250 ml 5% dextrose over 30 min without pre- or posttreatment hydration.

All patients received etoposide i.v. in 1,000 ml 0.9% saline over 1 h. Antiemetic therapy was given to all patients but was not standardized. Cycles were to be repeated every 28 days, provided that WBCs were $\geq$4,000 mm^3, platelet counts were $\geq$100,000 mm^3, and creatinine clearance was $\geq$60 ml/min. Responding patients received up to 5–6 cycles. Subjects with progressive disease and those showing either no major response after the third cycle or intolerable toxicity were removed from the study and further treatment was decided on an individual basis. Four to five patients were treated at each dose level until intolerable toxicity occurred in either two of four or three of five cases. To ensure detection of potentially cumulative toxicities, dose escalations were not planned in individual cases. Intolerable toxicity was defined as one of the following: hematologic toxicity (leukocytes, $\leq$1,500/mm^3; thrombocytopenia and/or anemia of higher than WHO grade 2), intractable nausea/vomiting for >48 h, renal toxicity above WHO grade 2 or a decrease in creatinine clearance to <40 ml/min, and other nonhematologic toxicity, except alopecia, of higher than WHO grade 2.

Table 1. Patients' characteristics

Number of patients		18
Median age (range)		58 (49–75) years
Performance status:		
	0	4
	1	13
	2	1
Residual disease:		
	bulky	11
	<2 cm	7
FIGO stage:		
	III	14
	IV	4

Results

All 18 consecutive patients who entered the study were evaluable for toxicity; 11 subjects with bulky disease and 7 with residual tumors measuring <2 cm were clinically evaluable for response. Clinical characteristics of the patients are reported in Table 1.

In all, 18 subjects received a total of 94 cycles (median, 6; range, 2–6/patient) of 350 mg/m^2 i.v. carboplatin and of i.v. etoposide given at doses of 210–390 mg/m^2 per course, fractionated over days 1–3. After the first cycle of 350 mg/m^2 i.v. carboplatin and i.v. etoposide given at doses of 210–330 mg/m^2 per course, toxicity defined as intolerable was not exceeded (Table 2).

Myelosuppression, whereby leukopenia was more profound than thrombocytopenia, was observed after the first cycle at doses of 350 mg/m^2 i.v. carboplatin and 390 mg/m^2 i.v. etoposide. At this dose level, the combination induced hematologic toxicity of grade 3 in two of five patients. Grade 3 leukopenia and grade 3 thrombocytopenia and leukopenia were observed in one patient each (Table 2); the leukocyte nadirs were 1,100 and 1,600 mm^3, and the thrombocyte nadir was 39,000/mm^3. These data

Table 2. Hematologic toxicity according to WHO criteria after the first cycle

Dose/schedule	Patients (*n*)	Toxicity	WHO grade (number of patients)				
			0	1	2	3	4
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 70 mg/m^2 i.v., days 1–3	5	Leukopenia	4	1	0	0	0
		Thrombocytopenia	5	0	0	0	0
		Anemia	4	1	0	0	0
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 90 mg/m^2 i.v., days 1–3	4	Leukopenia	2	1	1	0	0
		Thrombocytopenia	2	0	1	1	0
		Anemia	1	2	1	0	0
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 110 mg/m^2 i.v., days 1–3	4	Leukopenia	1	0	2	1	0
		Thrombocytopenia	3	0	1	0	0
		Anemia	3	0	1	0	0
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 130 mg/m^2 i.v., days 1–3	5	Leukopenia	0	2	1	2[a]	0
		Thrombocytopenia	3	0	1	1[b]	0
		Anemia	5	0	0	0	0

[a] Nadirs, 1,100 and 1,600 leukocytes/mm^3

[b] Nadir, 39,000 thrombocytes/mm^3

Table 3. Worst hematologic toxicities according to WHO criteria after the completion of treatment without dose modifications

Dose/schedule	Number of patients/ cycles/median	Toxicity	WHO grade (number of patients)				
			0	1	2	3	4
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 70 mg/m^2 i.v., days 1–3	5/26/6	Leukopenia	0	3	2	0	0
		Thrombocytopenia	4	1	0	0	0
		Anemia	3	2	0	0	0
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 90 mg/m^2 i.v., days 1–3	4/23/6	Leukopenia	0	0	3	1	0
		Thrombocytopenia	1	1	0	2	0
		Anemia	1	0	2	1	0
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 110 mg/m^2 i.v., days 1–3	4/21/6	Leukopenia	0	0	2	2	0
		Thrombocytopenia	1	1	1	1	0
		Anemia	1	1	2	0	0
Carboplatin, 350 mg/m^2 i.v., day 1 Etoposide, 130 mg/m^2 i.v., days 1–3	5/24/5	Leukopenia	0	0	0	4[a]	1[a]
		Thrombocytopenia	1	1	1	2[b]	0
		Anemia	3	2	0	0	0

[a] Nadirs, 900, 1,300, 1,500, 1,600 and 1,650 leukocytes/mm^3
[b] Nadirs, 38,000 and 39,000 thrombocytes/mm^3

Table 4. Nonhematologic toxicities according to WHO criteria after the completion of treatment

Toxicity	WHO grade (number of patients)				
	0	1	2	3	4
Serum creatinine	18	0	0	0	0
SGOT	9	8 (44%)	1	0	0
SGPT	10	7 (39%)	1	0	0
Serum bilirubin	16	2 (11%)	0	0	0
Nausea/vomiting	1	0	8 (44%)	9 (50%)	0
Alopecia	0	1 (6%)	10 (56%)	7 (39%)	0
Diarrhea	17	0	1 (6%)	0	0
Fever	17	0	1 (6%)	0	0

Data were obtained from 18 patients who completed a total of 94 cycles (median, 6/patient)

suggested that the maximum tolerated dose for phase II studies had been reached; therefore, no further dose escalations were performed. By this point, 5 patients had undergone a total of 24 cycles (median, 5/patient) of 350 mg/m^2 i.v. carboplatin given on day 1 and 130 mg/m^2 i.v. etoposide given on days 1–3 every 4 weeks.

The worst hematologic toxicity during all cycles was grade 4 leukopenia (900/mm^3) combined with grade 3 thrombocytopenia (38,000 mm^3) in one patient and grade 3 leukopenia (1,300/mm^3) combined with grade 3 thrombocytopenia (39,000/mm^3) in another subject. In three patients, grade 3 leukopenia with nadirs of 1,500, 1,600, and 1,650 leukocytes/mm^3 was observed (Table 3). After each course, the median nadirs of leukocytes and thrombocytes were seen on days 13 or 14 after the start of treatment. The median time to recovery of leukocytes to $\geq$4,000/mm^3 and of thrombocytes to $\geq$100,000/mm^3 ranged between days 26–28 and 16–20 after the beginning of treatment. The time to nadirs and the time to recovery were comparable after the first and all subsequent cycles.

At the dose levels tested, carboplatin/etoposide did not induce nonhematologic toxicities above WHO grade 2, except vomiting and alopecia. The worst nonhematologic toxicities per patient are shown in Table 4. Grade 3 vomiting and alopecia occurred in 50% and 39% of patients, respectively. An increase in SGOT and SGPT to grade 2 values was observed in one case. Diarrhea and fever of this degree occurred in one patient each. No renal toxicity or peripheral neuropathy occurred, and no clinical or audiographic evidence of ototoxicity was observed.

The results of this pilot study demonstrate that leukopenia is the dose-limiting toxicity of the combination carboplatin/etoposide. The recommended dose for phase II studies is 350 mg/m^2 i.v. carboplatin given on day 1 and 130 mg/m^2 i.v. etoposide given on days 1–3 every 4 weeks. At this dose level, myelosuppression is manageable and does not appear to be cumulative. Moreover, at the doses tested, carboplatin/etoposide induced 9 (50%) CRs and 12 (67%) objective responses (CRs + PRs) in 18 patients, with 95% confidence limits of 27%–73% for CRs and 45%–86% for objective responses. Three patients showed no change (NC) and three developed progressive disease (PD). In 11 subjects with bulky disease, 3 CRs and 5 overall responses were achieved; in 7 patients with residual disease measuring <2 cm, 6 CRs and 1 PR were obtained. In all, three subjects who had bulky disease and achieved clinical CRs after chemotherapy and four of six patients who had residual disease measuring <2 cm underwent second-look laparotomy. The CRs were confirmed in all three patients with bulky disease and in three of the four subjects with residual disease.

Discussion

In three prospective randomized trials in ovarian cancer, carboplatin showed antineoplastic activity comparable with that of cisplatin [1, 22, 28–30] while exhibiting statistically significantly less nephro-, oto-, neuro-, and gastroenteric toxicity [1, 23, 29–31]. Etoposide is one of the few active agents that induces 30% overall responses in cisplatin/alkylator-resistant ovarian cancer and displays

marked synergistic activity with carboplatin in experimental tumors [14, 18]. Evaluation of carboplatin and etoposide in first-line chemotherapy of ovarian cancer is therefore warranted, but the optimal dose needs to be defined because of the overlapping bone marrow toxicity. This trial was designed as a dose-escalating pilot study both to define the dose of etoposide that can be combined with a fixed dose of carboplatin and to obtain preliminary data on the antitumor activity of this combination in patients with advanced ovarian cancer that have undergone only surgical pretreatment. The moderately high carboplatin dose of 350 mg/m^2 was chosen because the dose intensity of platinum compounds is the most important chemotherapy-related factor in the induction of optimal responses [19].

The present study demonstrates that repeated cycles of carboplatin and etoposide may safely be given to patients with advanced ovarian cancer. The maximum tolerated dose for phase II studies is 130 mg/m^2 i.v. etoposide given on days 1–3 in combination with 350 mg/m^2 i.v. carboplatin every 4 weeks. At this dose level, myelosuppression is manageable and does not appear to be cumulative. Bone marrow recovery was always complete by day 28 and no treatment delays were required. Apart from alopecia and vomiting, no severe nonhematologic toxicities were induced. No renal toxicity, ototoxicity, or peripheral neurotoxicity was observed in this pilot study. The preliminary antitumor activity of carboplatin/etoposide was encouraging, resulting in 9 clinical CRs and 12 overall responses (67%) in 18 patients; 6 of the 9 clinical CRs were confirmed as pathological CRs by second-look laparotomy. These response rates are at least comparable with those previously reported in pilot studies for carboplatin and alkylators [9, 10, 13, 21] and for carboplatin/cyclophosphamide/Adriamycin combinations [5, 7] given with or without hexamethylmelamine [26, 27].

This study confirms the feasibility of treatment with carboplatin/etoposide at doses that result in acceptable response rates. The antineoplastic activity and tolerance of carboplatin/etoposide at the recommended dose is being investigated in a phase II study in patients with advanced ovarian carcinoma that was recently initiated by our group.

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