Primary chemotherapy in stage IV ovarian cancer.
A prospective phase II study

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Summary

Background and rationale: Non-curative surgical cytoreduction of advanced tumors is associated with increased proliferation of the remaining tumor cells. Thus, appropriate preoperative chemotherapy should prevent both cell proliferation and the increase of resistant cells. The aim of the present study was to evaluate the efficacy and toxicity of primary chemotherapy (P-CT) in previously untreated patients with stage IV ovarian cancer (OC).

Patients and methods: Thirty-four patients with stage IV OC were treated from January 1993 to April 2000 with P-CT. Eligibility criteria included: histologically or cytologically confirmed, unresectable stage IV OC and performance status ≤ 3. P-CT consisted of four courses of carboplatin, cyclophosphamide and epirubicin until October 1996, and paclitaxel, carboplatin thereafter. Surgery followed P-CT. After the operation patients received two further courses of chemotherapy that were tailored according to their individual response. Median (M) age was 61 years, range 32-73; median performance status was 2. A total number of 197 courses of CT were administered, median 5.7 per patient.

Results: Complete or partial response (CR, PR) was observed in 28 patients (response rate 82%, 95% CI: 65.4% to 93.2%), disease stability and progression (SD, PD) was observed in three and three patients, respectively. Median time to progression was 16.45 months (range 4.8-90.4+), median survival time was 28 months (range 4.5 - 90.4+); 1-year survival rate was 94%. Toxicity according to WHO: nausea and vomiting grade (G) 2, 30% of patients; gastrointestinal G 2-3, 20% of patients; alopecia G 3, 88% of patients; hematological G 3-4, 73% of patients; neurologic G 2, 12% of patients. Nine pathological CRs were observed.

Conclusion: Neoadjuvant treatment with CBDCA with either CTX and EPI or Taxol is feasible and shows activity in OC.

Key words: Stage IV ovarian cancer; Primary chemotherapy; Carboplatin; Cyclophosphamide; Epirubicin; Paclitaxel.

Introduction

Ovarian cancer is the second most common of the gynecological malignancies. The relatively asymptomatic nature of early disease and the lack of screening procedures, result in two-thirds of patients presenting advanced disease at the time of diagnosis [1]. High response rates may be expected initially with platinum-based chemotherapy after cytoreductive surgery.

Unfortunately, after a median number of 12 months, the majority of patients (75%) have disease relapse, with a 5-year survival rate less than 30% [1]. Long-term disease control is rare because of the development of drug resistance [2, 3].

For a decade, the combination of a platinum compound plus an alkylating agent has been considered the standard treatment for patients with advanced ovarian cancer. Meta-analyses have indicated that the addition of an anthracycline to a platinum compound and an alkylating agent increases both response rate and survival, but also toxicity [4-5]. Epirubicin, an analogue of doxorubicin with decreased cardiac toxicity, has demonstrated activity in platinum-pretreated patients with advanced ovarian cancer [6].

In recent years, the combination of cisplatin with taxanes is considered the standard treatment of advanced ovarian cancer [7]. Substituting cisplatin with carboplatin yields similar response rates and survival with decreased toxicity [8].

In spite of progress in the development of new drugs, patients affected by advanced ovarian cancer with bulky residual disease have a uniformly poor prognosis [2].

In recent years neoadjuvant chemotherapy has been increasingly applied to patients with breast cancer [9], gastro-esophageal cancer [10], head and neck cancer [11] and ovarian cancer [12]. Such cancers usually have micrometastatic deposits, which grow rapidly when primary tumor and draining lymph nodes are removed. Two main reasons for increased tumor growth after removal of the primary tumor are generation of antiangiogenic peptides by the primary tumor [13] and secretion of tumor inhibitory factors by bulky tumor [14].

According to this rationale, patients with stage IV ovarian cancer were treated with primary combination chemotherapy containing cyclophosphamide, carboplatin and epirubicin until October 1996 and with paclitaxel and carboplatin thereafter. Here we report treatment of 34 consecutive patients affected by stage IV ovarian cancer, treated with primary chemotherapy using a multimodality approach.

Patients and Methods

Patient Eligibility

Previously untreated patients with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage IV ovarian cancer were accrued in this phase II prospective study from July 1993 to April 2000. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of less than 4 and adequate bone marrow (WBC >4000/µL, platelets >100,000/µL), hepatic status (bilirubin level ≤ 1.5 mg/dL and AST ≤ double the upper normal limit), 24-hour creatinine clearance >60 ml and cardiac functions. Other eligibility criteria included: age > 18 and ≤ 75 years. Patients with other malignancies, other than curatively treated skin and cervical cancer, and active cardiovascular disease were excluded. Written informed consent, approved by the ethical committee, was obtained from each patient.

Prior to protocol entry, all patients had histological confirmation of their disease with Computed Tomography scan-guided biopsy or laparoscopy and underwent a complete work up to document the extent of disease, including clinical examination, complete blood cell count, plasma urea, creatinine and 24-hour creatinine clearance, electrolytes, liver function tests, serum CA 125 and carcinoembryonic antigen, electrocardiogram and CT scan of the abdomen and pelvis. X-rays of abnormal areas of bone scan uptake were performed; CT scanning was used to evaluate hepatic lesions. Before each subsequent course of treatment all patients had a further blood cell count, plasma urea, electrolytes, serum creatinine, GOT, GPT, alkaline phosphatase and bilirubin. In addition, a blood count was repeated on day 13 of each subsequent course of chemotherapy. Clinical tumor response and toxicity assessment were performed before each course of chemotherapy. Films or scans to document the response during therapy were repeated every 3 courses of chemotherapy or sooner, if the patient appeared to have disease progression.

Treatment Plan

The outpatient chemotherapeutic treatment was preceded by prophylactic intravenous premedication with 20 mg dexamethasone and 8 mg ondansetron. Carboplatin was administered at a dose of 300 mg/m² or at a free plasma concentration versus time curve (AUC) of 6 [15] by a short IV infusion on day 1. Cyclophosphamide was given 700 mg/m², diluted in 250 mL 5% glucose and delivered as a short intravenous (IV) infusion on day 1. Epirubicin was given 60 mg/m² by a 2-hour IV infusion on day 1. After October 1996 ten patients were treated with a combination of carboplatin and paclitaxel. Patients received premedication with dexamethasone 20 mg orally 12 and 6 hours before chemotherapy. Diphenhydramine 50 mg IV and ranitidine 50 mg IV were administered 30 minutes before chemotherapy. Carboplatin was administered at an AUC of 6 and paclitaxel was given by a 1-hour IV infusion at the dose of 175 mg/m². Therapy was repeated every three weeks for four courses if the patient had recovered from toxicity of previous chemotherapy and if there was evidence of response or disease stabilization. If ≥ grade 3 hematological toxicity occurred, administration of therapy was delayed until platelet counts were ≥ 100,000/µL and absolute granulocytes were ≥ 1,000/µL. If ≥ grade 3 gastrointestinal toxicity occurred the administration of chemotherapy was delayed until the optimal dose could be tolerated. NCI criteria for dose adjustment were used for neutropenia and thrombocytopenia. Radical surgery was planned after the fourth course of chemotherapy. After surgery, patients with complete or partial response received two further courses of the same chemotherapy. Non-responding patients received alterna-

tive drugs. Standard World Health Organization (WHO) criteria for assessing response and toxicity [16] were used.

Statistical Analysis

Time to progression was calculated from the time of protocol entry to the time of progression; survival was defined as the time elapsed between the start of treatment and the date of last follow-up evaluation or death. Both were assessed by means of the Kaplan and Meier product-limit method [17]. Analysis of data was performed on August 31, 2000.

Results

Patient Characteristics

Thirty-four patients were entered in this study between January 1993 and April 2000. All patients were evaluable for activity and toxicity. The characteristics of the 34 eligible patients are listed in Table 1. The median age was 62 years (range 18-74). ECOG performance status (PS) was 0-1 in 12 patients (35%), 2 in 17 patients (50%) and 3 in five patients (15%). Stage IV ovarian cancer was defined by pleural effusion with malignant cells (11 patients), lung metastases or mediastinal adenopathy (8 patients), bone metastases (3 patients), liver metastases (9 patients), pleura, bone and liver metastases (3 patients). Poorly, moderately or well-differentiated adenocarcinoma was observed in 70%, 21% and 9% of patients, respectively. All 34 patients received the protocol chemotherapy as primary treatment. A total of 197 courses of chemotherapy were administered, median 5.7 per patient (range 4-7). Twenty-four patients were treated with carboplatin-epirubicin-cyclophosphamide chemotherapy, while ten were treated with paclitaxel-carboplatin. Thirty patients received the full six courses of the protocol-chemotherapy, while four patients received four courses.

Table 1. — *Patient characteristics*

Characteristcs	No.	%
No. of patients	34	100
Age (years)		
median	62	
range	18-74	
Performance status (ECOG)		
0-1	12	35
2	17	50
3	5	15
Site of metastases		
pleura alone	11	32
liver alone	9	26
lung alone	8	24
bone	3	9
multiple sites	3	9
Histology		
serous cystoadenocarcinoma	24	70
mucinous cystoadenocarcinoma	5	15
mixed	2	6
endometroid	3	9
Grade		
well	3	9
moderate	7	21
poor	24	70

Table 2. — *Toxicity according to WHO criteria*

	WHO grade											
	0		1		2		3		4		Total	
	No.	%	No.	%	No.	%	No	%	No	%	No	%
Hematologic												
Leucopenia	4	11.8	3	8.8	7	20.6	16	47.1	4	11.8	34	100
Neutropenia	4	11.8	2	5.9	3	8.8	10	29.4	15	44.1	34	100
Thrombocytopenia	14	41.2	7	20.6	6	17.6	6	17.6	1	2.9	34	100
Anemia	9	26.5	14	41.2	2	5.9	9	26.5	0	0	34	100
Infection	28	82.4	0	0	2	5.9	4	11.8	0	0	34	100
Gastrointestinal												
Nausea and vomiting	2	5.9	22	64.7	10	29.4	0	0	0	0	34	100
Diarrhea	16	47.1	11	32.4	6	17.6	1	2.9	0	0	34	100
Neurotoxicity	28	82.4	2	5.9	4	11.8	0	0	0	0	34	100
Cutaneous												
Alopecia	0	0	0	0	4	11.8	30	88.2	0	0	34	100

Response and Survival

After a median follow-up of 23 months, 34 patients were evaluable for response and toxicity. Objective overall remission was observed in 28 patients, with a response rate (RR) of 82% (95% CI: 65.4% to 93.2%), with nine patients achieving a pathologically complete response (26%) and 19 a partial response (56%). Stable disease was observed in three patients (9%) and progression in three patients (9%). The median time to progression was 16.45 months (range 4.8-90.4+) (Figure 1). The actuarial median survival, for all patients was 28 months (range 4.5-90.4+) (Figure 2). One and two-year survival rates were 94% and 62%, respectively, and as of August 2000 11 patients (32%) were alive and progression-free between 4.8 and 90.4 months after starting treatment. Four patients underwent high-dose chemotherapy and peripheral blood progenitor cell transplantation after primary chemotherapy, surgery and two courses of postoperative chemotherapy.

Twenty-eight patients underwent exploratory laparotomy. Hysterectomy, bilateral salpingo-oophorectomy, omentectomy, random biopsy and peritoneal washing were performed in all of them. Pathological complete response was observed in nine patients. Nineteen patients exhibited a partial response to surgery. All were rendered disease-free after surgery. Three patients underwent surgical resection of liver metastases and one of them is alive 73 months following hepatic metastasectomy. Of the three patients with stable disease, two refused surgery, while the third patient was deemed inoperable and underwent a salvage chemotherapy. Three patients with disease progression were treated with topotecan chemotherapy.

Upon disease recurrence, a "second-look" operation was refused by two patients, while four patients were not operated on because of high operative risk.

Progression occurred in the following sites: peritoneum in nine patients, lung in three patients; bone in one patient, four patients progressed in the liver, while four patients had CA-125 increase. All responders and two patients with disease stability showed a substantial improvement of their ascites.

Toxicity

The side-effects associated with the chemotherapy protocol are listed in Table 2. The median WBC and platelet nadir occurred on day 14 (range 12-15), with a median hematological recovery on day 21. Hematological toxicity occurred in 60% of courses of chemotherapy. Dose reduction was required in 47 (24%) of the treatment cycles. The use of granulocyte colony-stimulating factor was not allowed during induction chemotherapy. There were six episodes of febrile neutropenia that required hospitalization. There was no treatment-related death. Fourteen (7%) courses of chemotherapy had to be delayed for one week because of gastrointestinal toxicity
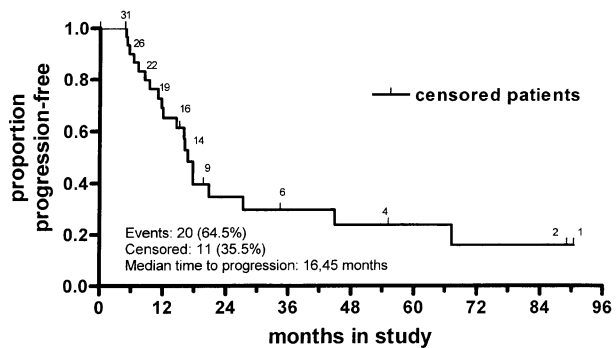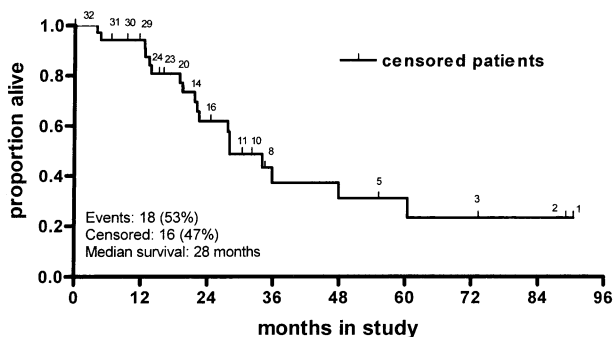

Figure 1. — Time to progression.

Figure 2. — Overall patient survival.

(diarrhea) and 34 (17%) for myelosuppression. Nausea and vomiting were mild due to the appropriate use of 5HT3 antagonists and dexamethasone. Grade 3 alopecia was observed in 88% of patients and could not be prevented by head hypothermia. Mild neurologic toxicity (sensory) was observed in 12% of the patients.

Discussion

Standard therapy for advanced epithelial ovarian cancer includes primary cytoreductive surgery followed by combination chemotherapy [18].

The importance of cytoreduction after surgical treatment of advanced ovarian cancer is critical for the prognosis: in a retrospective review [19], patients with no residual disease had a mean survival of 39 months compared with 29 months for residual disease of less than 0.5 cm, 18 months for residual disease of 0.6 to 1.5 cm, and 11 months for those who were not cytoreduced to below 1.5 cm. None of the last group of patients survived beyond 26 months. It is clear that very few patients with stage IV and some with stage III ovarian cancer may undergo radical surgery.

Moreover aggressive cytoreductive surgery has operative complications in the range of 5% [20]. Eighty-four women presenting stage IV ovarian cancer were retrospectively reviewed [21]. Primary surgical cytoreduction was attempted in all patients: 70% were left with residual disease > 1 cm, while only 30% of patients were optimally cytoreduced. Overall median survival was 18.1 months. Optimally cytoreduced patients had a median survival of 38.4 months, compared with 10.3 months for those with suboptimal residual disease. Such a low survival rate of the last group of patients could be due to increased proliferation of the remaining tumor cells associated with noncurative surgical cytoreduction. The enhanced proliferative rate that occurs after partial tumor removal makes an increase in the metastatic population by resistant phenotypes more likely [3]. Thus, appropriate preoperative chemotherapy should not only destroy cells made more sensitive by their kinetic alteration, but should also prevent cell proliferation and thus prevent an increase in resistant cells. Disappearance of circulating angiogenesis inhibitors by primary tumor removal could account for metastatic development [13].

Hunter and co-workers [22] reviewed a total of 58 separate studies including 6,962 patients to determine if maximum cytoreduction surgery benefits the survival of women with advanced ovarian cancer. The use of cisplatin chemotherapy resulted in an increased survival time of 53% (95% confidence interval, 35% to 73%; p<0.01). The dose intensity also had a significant impact on survival. This study concludes that cytoreductive surgery has only a small effect on the survival of women with advanced ovarian cancer and that the type of chemotherapy employed (i.e., cisplatin) is far more important.

Potential advantages of neoadjuvant chemotherapy appear to be a much more rapid improvement in the quality of life, a less expensive treatment program for the patients and, when surgery is ultimately performed,

an easier operation requiring shorter hospitalization. A group of Japanese researchers found, in a retrospective study, that a cohort of patients with advancd ovarian cancer, those who were treated with primary chemotherapy followed by optimal debulking surgery, had a better survival compared to patients who underwent surgery first [23].

On the other hand, in another retrospective analysis crude survival was higher when patients with advanced ovarian carcinoma were treated with primary chemotherapy instead of primary debulking surgery [24].

In our study nine pathological complete responses were obtained (26%) both in the abdomen and in metastatic sites and all these patients had a median survival of 28 months, showing a positive impact on disease-free and overall survival.

Prospective randomized trials comparing neoadjuvant chemotherapy to conventional therapy to determine quality of life experiences and cost/benefit outcomes should be now appropriate for women presenting with advanced ovarian cancer.

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