GYNECOLOGIC ONCOLOGY 58, 68–73 (1995)

Carboplatin (CBDCA)–Hexamethylmelamine (HMM)–Oral Etoposide (VP-16) First-Line Treatment of Ovarian Cancer Patients with Bulky Disease: A Phase II Study

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Received October 4, 1994

Hexamethylmelamine (HMM) and oral etoposide (VP-16) have shown to be active against platinum-resistant epithelial ovarian cancer. On this basis a three-drug regimen including carboplatin (CBDCA) plus HMM and oral VP-16 was tested in previously untreated ovarian cancer patients with tumor size >2 cm. Since October 1991, 29 chemotherapy-naive ovarian cancer patients with tumor larger than 2 cm (20 stage III and 9 stage IV) have been treated for a total of 153 courses. CBDCA was administered iv on Day 1. The dose was individualized using the Calvert formula (the target dose was AUC=5). VP-16 was administered orally at the dose of 50 mg/m² Days 1–14, HMM at the dose of 150 mg/m² po Days 14–28. Therapy was repeated every 28 days for a total of 6 courses. In order to avoid severe leukopenia and delays in the treatment administration, G-CSF 5 μg/kg/day sc Days 8–14 (or until postnadir recovery of neutrophil count >10,000/mm³) and Days 22–28 was administered. All patients were evaluable for toxicity. No treatment-related deaths occurred. Myelotoxicity was the main side effect. It was grade 3–4 in a total of 13/29(45%) patients. One patient discontinued treatment after the first course due to HMM-related gastrointestinal toxicity. The actual delivered dose intensity was 89% of the planned dose. At the time of this analysis (April 1994) 26 patients are evaluable for response. Fifteen patients achieved a clinical complete remission and 9 a partial response for a 92% overall response rate. Fourteen patients accepted second-look laparotomy. We observed 11 pathological complete regressions (42%; 95% CI, 21–63). At a median follow-up of 16 months 3 deaths have occurred. Only 2 patients with NED at second-look laparotomy have relapsed. We stopped the accrual since the 95% confidence interval of the pCR-rate observed exceeded 20%. This new first-line regimen seems to be highly effective in patients with poor-prognosis advanced ovarian cancer, although the data are not yet sufficiently mature for a final analysis of time to progression and overall survival. © 1995 Academic Press, Inc.

INTRODUCTION

Platin-based therapy represents a landmark in the treatment of patients with advanced ovarian carcinoma [1]. However, despite the high response rate achieved, this treatment cannot cure most patients with advanced disease; Hoskins *et al.* [2] recently reported 10-year overall and disease-free survivals of 8 and 4% respectively in epithelial ovarian cancer. Residual disease larger than 2 cm represents by far the most predictive parameter of a poor prognosis.

An overview [3] of randomized clinical trials on chemotherapy in advanced ovarian cancer found a significant survival advantage for patients treated with a cyclophosphamide, doxorubicin, and cisplatin (CAP) regimen, over those treated with cisplatin and cyclophosphamide alone (CP), but the total doses of drugs were higher in patients receiving the three-drug combination. Since comparison of cisplatin and carboplatin when given either as single agents or in combination showed no difference in terms of survival, an international trial, Icon-2 (International collaborative ovarian neoplasm study), was started to compare the CAP regimen with optimal dose carboplatin because it is still questionable whether the addition of other drugs improves long-term results achievable by platinum analogs alone.

New drugs with confirmed non-cross-resistance with cisplatin are needed to increase the rate of long-term survivors and of cure in advanced ovarian cancer patients.

Hexamethylmelamine (HMM) cannot be considered a new drug in the treatment of ovarian cancer patients. It has been used in clinical trials since 1969 and has been shown to have single agent activity similar to melphalan in previously untreated patients with advanced ovarian cancer [4]. In 1991 Manetta *et al.* reported that it could also induce long-term remissions in patients resistant to cisplatin-based chemotherapy [5]. Much more interestingly, there have been several reports showing a clear advantage of H-CAP (with the addition of HMM to CAP) over cisplatin-based regimens without HMM in terms of both progression-free interval and overall survival [6].

Etoposide has not demonstrated an encouraging therapeutical activity in platin-resistant ovarian cancer patients, when administered intravenously. However, in view of its schedule

0090-8258/95 $12.00

dependency [7], an increase of its efficacy in ovarian cancer patients could be hypothesized after low-oral-dose administration, as confirmed by reports in SCLC and breast cancer patients [8, 9].

Preliminary reports show that prolonged oral etoposide is quite active in platinum-resistant ovarian cancer patients [10, 11].

On the basis of these considerations we started a phase II study testing a combination of hexamethylmelamine and oral VP-16 in heavily pretreated ovarian cancer patients in April 1991 [12]. Following the very encouraging preliminary results of this study (1 clinical complete and 2 partial responses among the first 6 enrolled patients), we decided to start a phase II trial adding HMM + oral VP-16 to standard dose carboplatin in chemotherapy-naive ovarian cancer patients with bulky disease. We also administered granulocyte colony-stimulating factor since it has been shown to reduce the severity and duration of leukopenia induced by chemotherapy [13] and could allow higher doses of chemotherapy agents without incurring significant myelosuppression.

Only patients with bulky disease were included in this trial because their expected pathological complete response rate is so low (<20%) that even a minor increase in the response rate could be more easily statistically detected.

PATIENTS AND METHODS

Patient Population

Twenty-nine patients with histologically confirmed diagnosis of epithelial ovarian cancer were entered into the trial between October 1991 and February 1994, after receipt of informed consent and central pathology review. Median age was 61 (range 46–73). All had advanced disease (20 stage III and 9 stage IV, FIGO) with residual tumor to primary surgery larger than 2 cm. Additional inclusion criteria were an Eastern Cooperative Oncology Group performance status (before primary surgery) of 0, 1, or 2; patient age between 18 and 75 years; life expectancy of at least 3 months; normal hematologic indices; and renal and liver function tests within normal limits. Patients were excluded if they had had any other cancer within 5 years, except for superficial skin carcinoma or carcinoma *in situ* of the cervix, or if they suffered from serious intercurrent medical problems.

Table 1 lists the main patient characteristics.

TABLE 1
Patient Characteristics

Age	
Median (range)	6 (46–73)
ECOG PS	
0–1/2	19/10
FIGO stage	
III	
<5 cm	11
5–10 cm	5
>10 cm	9
IV	4
Histology	
Serous	16
Endometrioid	3
Undifferentiated	7
Mucinous	1
Mixed	2
Grading	
1/2/3	6/10/13
Total	29

Primary Surgery

All patients who underwent surgery before the initial chemotherapy were included regardless of the type of surgery performed. Of the 29 eligible patients, a completed bilateral salpingo-oophorectomy, hysterectomy, and an infracolic omentectomy were performed in 11 (optimal surgery). Five patients had a hysterectomy and bilateral salpingo-oophorectomy, with no omentectomy; and the remaining 13 patients, who were inoperable, underwent a biopsy only.

Chemotherapy

All patients were scheduled to receive 6 courses of chemotherapy. The first course was started within 6 weeks of the surgical procedure. Chemotherapy consisted of iv carboplatin administered in normal saline over 30 min, repeated every 4 weeks, on an outpatient basis, VP-16 50 mg/m^2 orally Days 1–14 and hexamethylmelamine 150 mg/m^2 orally Days 15–28. The dose of carboplatin was individualized according to the Calvert's formula: Dose (mg) = AUC(mg/ml × min) × (GFR[ml/min]+25). The target AUC was 5. The creatinine clearance was measured at each course to determine the carboplatin dose. In order to avoid severe leukopenia and delays in the treatment administration, G-CSF 5 μg/kg/day sc Days 8–14 (or until postnadir recovery of neutrophil count >10,000/mm^3) and Days 22–28 was administered.

Total WBC, hemoglobin, and platelet counts were performed twice a week between courses. Etoposide and/or hexamethylmelamine were discontinued if the patient experienced grade 4 leuko- or thrombocytopenia, or grade 3–4 major organ toxicity and the doses of the three drugs were reduced by 25% for subsequent courses. For patients who required dose reduction, the dosages were not reescalated. A maximum of two 25% dosage reductions were permitted. Patients who continued to experience dose-limiting toxicities after two dosage decreases were removed from the study. Drug administration was postponed by 1 week if there had not been full hematologic recovery at 4 weeks (WBC > 4,000; platelets > 100,000). If after a 1-week delay grade

1 leuko- or thrombocytopenia persisted, then a 25% dose reduction was performed. The patient was withdrawn from the study if grade >2 myelotoxicity persisted after 2 weeks from the date of recycling.

Response Evaluation

We considered the rate of pathological complete responses (pCR) as the main endpoint of the study. We also evaluated the rate of clinical objective responses (cOR), the time to progression (TTP), the relapse-free survival (RFS), and overall survival (OS).

Evaluation of clinical response was performed after the sixth cycle, unless there was clinically evident progression before this time. The evaluation consisted of clinical examination, routine laboratory tests, and serum tumor markers determination (CEA, TPA, CA-125, CA-15.3), and a repeat of the initial imaging technique if it had been positive.

A clinical complete response (cCR) was defined as disappearance of all evidence of the tumor after clinical restaging. A clinical partial response (cPR) was a 50% or greater decrease in the sum of the products of the diameters of all measurable lesions, or a 50% decrease in the diameter of unidimensional lesions with no increase in size of any existing lesions. Clinical progressive disease (cPD) was the appearance of new lesions, effusions, or ascites, or a 25% or greater increase in either the products of the diameters of any bidimensional lesions or diameter of any unidimensional lesion. Clinical stable disease (cSD) did not meet the criteria for either a cPR or a cPD.

Patients with cSD at the sixth course or who developed cPD during chemotherapy were taken off the study but were not excluded from the analysis. They received a non-cross-resistant chemotherapy. Patients with cPR at sixth course continued the treatment until evidence of disease progression, or for a maximum of 12 courses. Patients with cCR at the end of the sixth course underwent second-look laparotomy. This consisted of xiphopubic incision, assessment of the size of macroscopic residual tumor, if present, and its removal when feasible; multiple biopsies of suspected lesions, and of previously involved areas, and random biopsies of high-risk regions were taken. Multiple peritoneal washings were performed when no macroscopic tumor was found. In patients who had not been submitted to optimal primary surgery, remaining surgical procedures were performed, consisting of hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and appendectomy as appropriate.

Patients with pathological (pCR) or surgical complete response (sCR), or partial responders having less than 5 mm residual tumor received three additional courses of intraperitoneal chemotherapy, consisting of a carboplatin–interferon-α 2b combination; those partial responders with a larger persistent tumor received an additional 6 courses of the same treatment. Patients with stable or progressive disease at laparotomy received non-cross-resistant systemic chemotherapy.

We defined a pCR as the absence of macroscopic and microscopic disease at laparotomy. A patient was considered in sCR if the residual tumor at second-look laparotomy was completely removed by the surgeon. A pathological partial response (pPR) was the laparotomic finding of a 50% or greater decrease in the sum of the products of the diameters of all measurable lesions, or a 50% decrease in the diameter of unidimensional lesions with no increase in size of any existing lesions. Patients with laparotomic finding of less than 50% decrease in the tumor size were considered as having stable disease. Finally, the patient was considered in progression if a >25% increase in tumor size and/or appearance of new tumor lesions occurred.

TTP was measured from the date of entry to the date of first documentation of relapse. RFS was defined as the interval between the documentation of pCR achievement and that of relapse. OS was measured from the date of entry to the time of death.

Statistical Methods and Study Design

All patients were evaluated on an "intention to treat" basis. Therefore, early death, withdrawal for toxicity, refusal of treatment, ineligibility, protocol violation, lost to follow-up, etc. did not justify exclusion from analysis.

Since we considered a pCR rate <20% as unacceptable and chose 40% as target activity level, according to Simon's two-stage minimax design, the accrual stops if <4/18 pCRs occurred ($\alpha = 0.05$, $\beta = 0.20$) [14]. We planned a maximum sample size of 33 patients. This combination would have been rejected if <10/33 pathological complete responses were achieved.

Time to progression (TTP) and overall survival (OS) were calculated with the method of Kaplan–Meier [15]. Data were stored and analyzed with the Systat software package [16].

RESULTS

Toxicity

All patients were evaluable for toxicity. No treatment-related death occurred. World Health Organization (WHO) grading was used to assess both hematologic and nonhematologic toxicity. Myelotoxicity is listed in Table 2, as percentage of the total courses delivered. Of the total 153 courses of chemotherapy assessed, 8 (5%) were delayed because of myelosuppression, despite G-CSF administration. In 13 courses the oral administration of drugs had to be discontinued because of grade 4 neutropenia (6) or thrombocytopenia (7). No patients developed sepsis. In a total of 28 courses the dose of carboplatin was reduced by 25% and in 3 by 50%. In treated patients we observed grade 4 neutropenia and thrombocytopenia in 3 and 4 patients, respectively. One patient with a partial response was removed from the study after the fourth course of chemotherapy because of

TABLE 2
Toxicity (% of total courses)

	WHO grade				
	0	1	2	3	4
Neutropenia	31	23	30	12	4
Thrombocytopenia	37	18	24	16	5
Anemia	46	24	18	10	2
Vomiting	23	44	23	8	2
Abdominal pain	52	26	14	6	2
Alopecia	16	30	38	12	4
Neurotoxicity	74	18	8	—	—

persistent neutropenia. The actual delivered dose intensity of carboplatin was 89% of the planned dose. Although the delivered dose of carboplatin ranged between 290 and 420 mg/m^2, we did not observe a clear correlation between the delivered dose and myelotoxicity. Grade 3–4 neutropenia or thrombocytopenia occurred in 6/16 patients receiving $\leq$ 350 mg/m^2 of carboplatin compared to 5/13 in those receiving higher doses.

Nonhematologic toxicity was rarely relevant. Gastrointestinal side effects were almost always mild or moderate. Only one patient discontinued treatment at first course because of severe nausea and abdominal pain related to hexamethylmelamine administration. Nine patients reported peripheral sensory neuropathy (6 mild, 3 moderate), and four patients suffered from grade 1 or 2 mucositis. A transient increase of creatinine serum levels was observed in one patient.

Response

At the time of this analysis (April 1994) 26 patients are evaluable for response. Twenty-one had clinically or radiologically documentable disease, and only four increased CA-125 serum levels. Only one woman had no clinically evaluable disease at the beginning of chemotherapy. At the end of the planned 6 courses of chemotherapy, 15 patients showed no clinical or laboratory evidence of disease. In an additional 9 patients a partial response was achieved for a 92% overall response rate. One patient showed no change at restaging and 3 progressed before the end of chemotherapy. Fourteen patients accepted a second-look laparotomy. We observed 11 pathologically complete regressions (42%; 95% CI = 21–63). Five occurred in patients who had biopsy only at first laparotomy. Table 3 lists responses according to main pretreatment variables. At a median follow-up of 16 (3-29) months 3 cancer-related deaths occurred (Fig. 1). Median survival has not yet been reached, and the 2-year actuarial probability of survival exceeds 80%, as does the 2-year DFS. Only 2 patients of the 11 with NED at second-look laparotomy have relapsed (Fig. 2). We stopped the accrual since the lower limit of the 95% confidence interval of the pCR rate observed exceeded 20%.

TABLE 3
Response

	No. of pts (%)		
	pCR	cCR	cPR
FIGO stage			
III			
<5 cm	6/10 (60)	9/10 (90)	10/10 (100)
5–10 cm	1/4 (25)	2/4 (50)	4/4 (100)
>10 cm	1/3 (33)	1/3 (33)	3/3 (100)
IV	3/9 (33)	3/9 (33)	7/9 (77)
Grading			
0–1	8/18 (44)	11/18 (61)	18/18 (100)
2	3/8 (37)	4/8 (50)	6/8 (75)
Age			
<65	8/16 (50)	10/16 (62)	16/16 (100)
>65	3/10 (30)	5/10 (50)	8/10 (80)
Total	11/26 (42)	15/26 (58)	24/26 (92)

Note. pCR, pathological complete response; cCR, clinical complete response; cPR, clinical partial response.

DISCUSSION

Ovarian cancer patients with bulky residual tumor after first laparotomy show a very low percentage of pathological complete remissions at second-look laparotomy following first-line chemotherapy, and most of these patients will relapse. Furthermore, survival is impaired by the extent of disease before chemotherapy. Young *et al.* [17] summarized nine reports in which median survival is based on primary cytoreductive surgery to less or greater than 2 cm of residual disease. Mean survival was 29.4 months in the optimally cytoreduced group and 13.4 months in the group in which cytoreduction was suboptimal. Although the CAP regimen seems to have a slight advantage in terms of second-look

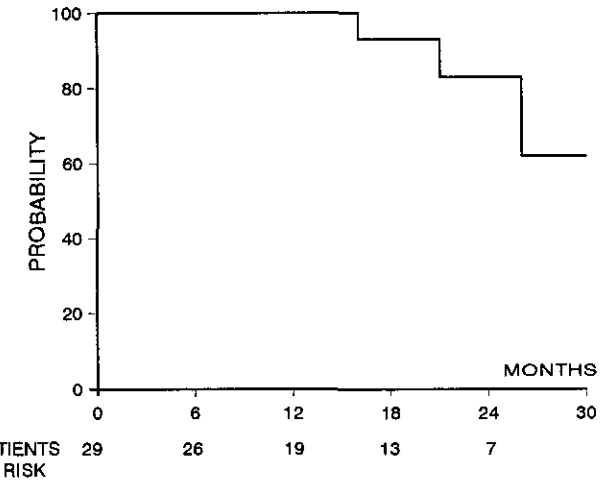

FIG. 1. Survival: Total, 29; fail, 3.

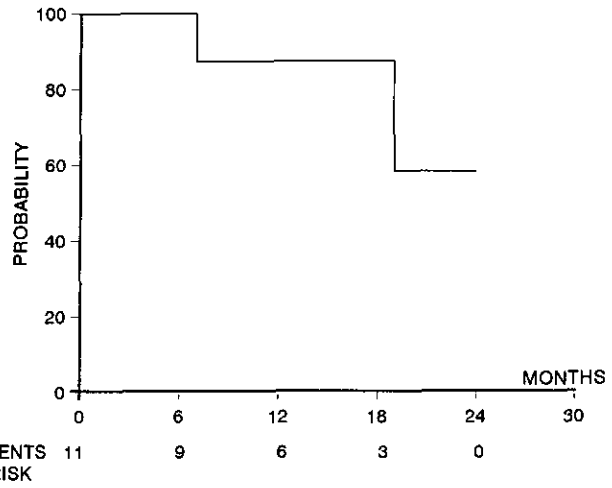

FIG. 2. Relapse-free Survival: Total, 11; fail, 2.

operation and survival over CP, the true benefits of doxorubicin have not yet been demonstrated. In any case, the results of the standard chemotherapy regimens are very discouraging in these patients, so further efforts are required to improve them. The large international trial, Icon-2, which was set up to assess whether CAP regimen is better than optimal dose carboplatin, will not be able to significantly affect these results. In fact, even if a moderate advantage of CAP over carboplatin is found, it would have very little impact on the outcome of these patients.

We believe that further phase II trials should be carried out in patients with advanced ovarian cancer, to find a combination able to more strongly improve pCR rate and survival of these patients. We believe that patients with larger tumor after first surgery should receive a different first-line treatment from those with minimal tumor size. We believe that given the basic role of platinum analogs in the treatment of this disease, and assuming that cisplatin and carboplatin are equally effective, drugs with a true non-cross-resistance with the platinum analogs should be chosen.

The aim of our study was to assess whether the addition of hexamethylmelamine and oral etoposide, which had been shown to be effective in patients truly resistant to platinum analogs, could significantly improve the results achievable by carboplatin alone. We excluded the cyclophosphamide since we considered it certainly cross-resistant with platin analogs. It is likely that a good response rate in platinum-refractory patients may be achieved after high-dose administration of antracyclines [18]. However, only low–moderate doses could be administered in combination with carboplatin in view of the strong myelotoxicity of both.

We chose a moderate dose of carboplatin since a retrospective analysis of the relationship between dose and response rate failed to show significant advantages when delivered doses exceed AUC 5-7 [19].

Our results, although still preliminary, look promising. The combination caused severe toxicity, either hematologic or nonhematologic, in a very low percentage of patients. No treatment-related deaths occurred, and no septic or hemorrhagic epidodes were observed, although in 13 courses grade 4 neutropenia or thrombocytopenia occurred. It is interesting to point out that almost 90% of the planned dose of carboplatin was actually delivered to the patients. Also gastrointestinal side effects were generally mild; in fact, only one patient had to discontinue the treatment because of them.

The overall efficacy of the treatment was good. We achieved a more than 40% pCR rate, with a lower limit of the 95% confidence interval exceeding 20%. These results seem to compare favorably with those achieved in the past by standard cisplatin-based regimens in ovarian cancer patients with bulky tumor at the beginning of chemotherapy, especially if we consider that more than half of our patients had received no cytoreduction at first laparotomy. Although the short follow-up prevents us from drawing any conclusion about the long-term survival rate and the possibility of cure, it is encouraging that we obtained a 2-year DFS and overall survival exceeding 80%.

The therapeutic role of paclitaxel when administered in combination with cisplatin as front-line treatment has been recently emphasized. This combination achieved a 25% pCR rate in patients with suboptimal first surgery (residual disease >1 cm) with a median time to progression of 18.1 months [20]. We must remark that our data, although concerning a very small ovarian cancer patient population, appear more promising, since the pCR rate exceeded 40% and median TTP exceeds 2 years. In our opinion the efficacy of paclitaxel has been overestimated in true platinum-resistant ovarian cancer patients. In fact the response rate in the Canadian/European study [21] was only 11.9%. Also data concerning toxicity seem to favor our regimen compared to cisplatin–paclitaxel combination. In fact, the evidence of very uncommon severe toxicity confirms that the three drugs included in our combination have nonoverlapping toxicity, while the paclitaxel–cisplatin combination showed higher toxicity than the standard cisplatin–cyclophosphamide treatment [21]. In a phase I/II study testing the combination of carboplatin and paclitaxel, conducted by Ozols *et al.* [22], it was concluded that these two drugs can be combined with acceptable toxicity over the full therapeutic dose range of each drug. However, although the tolerance of this combination seems better than that of the cisplatin–paclitaxel regimen, a similar therapeutic efficacy can be expected.

Several questions remain about the use of G-CSF to improve chemotherapy-induced neutropenia, including the optimal dose of this drug and the best schedule of administration with respect to chemotherapy. With regard to dose, it is unlikely that more than 5 μg/kg/day of G-CSF can achieve a better prevention of chemotherapy-related neutropenia, as suggested by the most recent trials [23, 24]. The schedule of administration (Days 8–14 and 22–28) was chosen to

avoid too long an overlap with VP-16, and to permit an adequate neutrophil recovery on Day 29. Our results seem to confirm that this schedule assures good protection from severe neutropenia (it was grade 4 in only 6 courses) and permitted chemotherapy recycling at the planned intervals in all but 8 courses. However, further efforts should be made to improve the efficacy of the hematopoietic growth factors. The introduction of IL-3 into clinical practice seems a further step ahead. Several authors reported better myeloprotection after simultaneous administration of IL-3 and G or GM-CSF than after these molecules alone [25, 26].

In conclusion, this new first-line regimen seems to be a very promising therapeutical approach for patients with poor-prognosis advanced ovarian cancer, in view of the good tolerance and the high pCR rate. Also the preliminary survival data, although not yet sufficiently mature for a final analysis, seem encouraging. A randomized trial comparing this combination to standard cisplatin/carboplatin-based regimens is needed to determine the best first-line-treatment in this subgroup of ovarian cancer patients.

ACKNOWLEDGMENT

We thank John Perchard for proofreading the English of the manuscript.

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