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Original Paper

Carboplatin Alone Compared With its Combination With Epirubicin and Cyclophosphamide in Untreated Advanced Epithelial Ovarian Cancer: a Hellenic Co-operative Oncology Group Study

D.V. Skarlos,[1] G. Aravantinos,[1] P. Kosmidis,[2] N. Pavlidis,[3] K. Gennatas,[4] M. Beer,[5] N. Mylonakis,[2] P. Makrantonakis,[6] G. Klouvas,[3] S. Karpathios,[7] H. Linardou,[1] C. Konstantaras[6] and G. Fountzilas[6]

[1]Agii Anargiri Cancer Hospital, Kaliftaki Kifisia, Athens; [2]Metaxa Cancer Center, Botasi 51 Piraeus; [3]Ioannina University Ioannina 45 110; [4]Areteion University Hospital, Athens; [5]HeCOG office Mesogion 82, Athens; [6]Ahepa University Hospital, S. Kiriakidi 1 Thessaloniki; [7]Alexandra Hospital, V. Sofias 80, Athens, Greece

We compared, in a multicentric randomised prospective study, the efficacy and toxicity of carboplatin 400 mg/m^2 as a single agent (CB) to a combination of carboplatin 300 mg/m^2, epirubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (CB-EC) in advanced ovarian cancer patients. The treatment was scheduled to be administered every 3 weeks for six courses. Following initial laparotomy and cytoreductive surgery, 130 previously untreated patients entered the study. 73 patients were treated with carboplatin alone while 57 received the combination chemotherapy. In the majority of the patients, the regimens had to be given every 4 weeks due to myelosuppression. Nausea, vomiting and alopecia were more severe in the CB-EC arm. Overall, clinical complete response was observed in 73 (56%) and partial response in 20 (15%) patients. The median time to progression was 16.89 months and median survival was 29.54 months. No significant differences in response rate, time to progression, disease-free survival and overall survival were observed between the two treatment arms. The prognostic role of residual disease after initial surgery, complete remission at second-look laparotomy, tumour stage and performance status was confirmed.

Key words: ovarian cancer, carboplatin-based chemotherapy
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INTRODUCTION

Of all gynaeological cancers, ovarian cancer is the major cause of death, with a 70% mortality rate [1]. The initial diagnosis is of advanced disease, i.e. FIGO stages III and IV, in approximately 70% of patients [2, 3]. Since higher response rates and longer disease-free intervals have been observed when chemotherapy follows initial cytoreductive surgery, this sequence of treatments is now recommended for women with advanced epithelial ovarian cancer (AEOC) [4]. Response rates can reach up to 75% with this multimodal approach. However, despite high initial response rates, most patients eventually die, the proportion of long-term survivors among patients with AEOC being around 10%, with a median survival of 25–27 months [5].

Various alkylating agents, hexamethylmelamine and anthracyclines have shown activity in AEOC. However, despite occasionally high response rates, the complete response (CR) rate and survival are disappointingly low [6–8]. Cisplatin alone or its combination either with cyclophosphamide, or with doxorubicin and cyclophosphamide have proven to be very active in ovarian cancer, achieving a 60–80% overall response rate with approximately 50% clinical CR (cCR) and 20% pathologically confirmed CR (pCR). In addition, patients treated with cisplatin-based chemotherapy show a significant prolongation of overall survival [9, 10]. With 15–20% disease-free survival (DFS) in advanced disease, cisplatin is currently

Correspondence to D.V. Skarlos at the Hellenic Co-operative Oncology Group HeCOG, Mesogion 82, 115 27 - Athens, Greece.
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considered to be the most active cytotoxic drug in ovarian cancer; alone or combined with an alkylating agent, it is currently accepted as standard chemotherapy in this disease [5, 11].

However, the majority of patients with AEOC are in the sixth decade of their life. Apart from their rather advanced age, they may have additional severe medical problems, such as cardiac or renal dysfunction. Their tolerance to some troublesome side-effects such as nausea, vomiting and neurotoxicity, or to the forced hydration and diuresis accompanying cisplatin administration is poor [12]. The escalation of cisplatin dosage, which possibly increases response rate, is associated with unacceptable, mainly neurological toxicity and some myelotoxicity. Thus, chemotherapy is often interrupted or delayed and this might compromise the therapeutic results [13, 14].

Carboplatin (CBDCA), an analogue of cisplatin, is devoid of serious and frequent side-effects other than dose-limiting myelosuppression, and can be easily administered without prehydration on an outpatient basis [15]. In phase III studies, 400 mg/m^2 carboplatin have proven to be at least as effective as 100 mg/m^2 cisplatin in patients with AEOC [16, 17].

The combination of CBDCA with cyclophosphamide, or cyclophosphamide and epirubicin, seems to yield response and survival rates comparable to those of monotherapy [18–20]. Since no randomised comparisons between CBDCA monotherapy and its combination with other active drugs have been reported, the Hellenic Co-operative Oncology Group decided to conduct the present study in order to compare the efficacy and toxicity of CBDCA alone versus its combination with epirubicin and cyclophosphamide in advanced ovarian cancer. A secondary objective was to assess the feasibility of a 3-weekly administration, at the dose of 400 mg/m^2 as a single agent, and 300 mg/m^2 in combination.

PATIENTS AND METHODS

Previously untreated patients with ovarian carcinoma of epithelial origin (FIGO stages IIc, III and IV according to the surgical and cytological findings) entered the study [3]. All had undergone an initial laparotomy in order to reduce the tumour mass as much as possible, and to determine accurately the extent of the disease. The largest diameter of residual disease was registered. In the absence of macroscopic residual disease, peritoneal washings and multiple biopsies were examined for the presence of malignancy.

One to 2 weeks after surgery, the patients were to receive six cycles of chemotherapy. To be eligible, patients with histologically or cytologically confirmed epithelial ovarian cancer had to have an ECOG performance status (PS) ≤ 3 and adequate haematological [white blood cells (WBC) $\leq 4.000/mm^3$, platelet $>100\,000/mm^3$ and haemoglobin ≥ 10 g/dl] and renal function (creatinine clearance ≥ 50 ml/min). Ten to 20 days after the end of the last cycle of chemotherapy, patients were re-evaluated and those deemed clinically to be in complete remission were advised to undergo a second-look laparotomy. The second-look surgery included a complete re-examination of the abdominal cavity. Any macroscopic disease found during this operation was removed where possible. Peritoneal washings and multiple biopsies were obtained from predetermined sites and adherences were removed.

Further treatment of patients with less than complete remission was left to the individual physician's decision.

Chemotherapy

Before the initiation of chemotherapy, patients gave signed informed consent according to the Helsinki declaration and to our institutional policies.

Patients were then randomised to receive either CBDCA 400 mg/m^2 (CB) or combination treatment with CBDCA 300 mg/m^2, epirubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (CB-EC) intravenously (i.v.) every 3 weeks for six courses. CBDCA was administered by a 1-h infusion in 250 ml 5% dextrose, while epirubicin and cyclophosphamide were given by rapid infusion. Treatment was started on the day of randomisation or on the following day.

Thirty minutes prior to the initiation of chemotherapy, patients received metoclopramide 30 mg i.v., followed by 10 mg orally every 8 h for 3 days. In 1991, patients with nausea and vomiting refractory to treatment during the first course received an alternative anti-emetic prophylaxis in the following courses, with dexamethasone, 8 mg and ondansetron 8 mg, 30 min before starting chemotherapy, followed by ondansentron 8 mg orally every 8 h for the 3 consecutive days.

Dose modifications and treatment delays

Dose modifications were adjusted according to the white blood and platelet count as well as to the clearance of creatinine. Thus, if WBC count was $\geq 3500/mm^3$ and platelets $\geq 100\,000/mm^3$, no dose modification was made. If WBC count was between 3000 and 3500/mm^3 and platelets between 75 000 and 100 000/mm^3, 75% of the dose was administered. If WBC count was less than 3500/mm^3 and/or platelets less than 75 000/mm^2 then treatment was delayed until recovery.

CBDCA was also adjusted according to the clearance of creatinine. Thus, if creatinine clearance was >50ml/min, then no dose modification was made. A 50% reduction of the dose was performed if clearance of creatinine was between 30 and 49 ml/min. Treatment was postponed until recovery if creatinine clearance was found to be <30 ml/min.

Response definition

A cCR was defined as a complete disappearance of all clinically detectable disease for at least 4 weeks; a partial response (cPR) was as a reduction by 50% or more of all measurable or evaluable lesions and a reduction of all non-measurable tumours in the absence of new lesions. Stable disease (SD) was defined as a reduction by 20–50% for the same duration; progressive disease (PD) was defined as an increase in any lesion or the appearance of new lesions.

pCR was defined as absence of disease at second-look surgery, including negative peritoneal washings and multiple biopsies.

Periodical examination and evaluation

Blood count, serum creatinine level, history of symptoms and adverse reactions were registered before each treatment course. The WHO scale for toxicity grading was used wherever applicable [21]. Evaluation of blood count, serum creatinine level for full blood chemistry, including plasma levels of CA-125 antigen, were performed on the day of treatment. If patients had a febrile or haemorragic event, WBC and platelet count was performed at the time of the episode. Response assessment was repeated every two cycles. Time to progression (ttp) was calculated from the day of randomisation to the day renewed progression or recurrence of the disease was documented, and survival from the day of randomisation to

the date of death. Relapse-free survival (RFS) was calculated from the time of documented PR or CR to the day of recurrence, while DFS from the time of the achieved CR to the day of recurrence. Patients who had no recurrent tumour or were alive on the day of the last update were censored in these calculations.

Dose intensity

Dose intensity (DI) was defined as the amount of drug delivered per unit of time, expressed as mg/m^2/week. Relative dose intensity (RDI) was defined as the amount of drug delivered per unit of time relative to the planned dose of CBDCA or, for the combination regimen, the decimal fraction of the ratio of the average dose intensity of all drugs [22].

Statistical analysis

This study was designed taking into consideration that 5-year survival rate of patients with AEOC treated with CBDCA alone is expected to be approximately 20% [23] and anticipating a 20% survival difference for combination arm. Therefore, we required 59 patients for each arm based on a 5% one-sided log rank comparison with 80% power [24]. The required total number of patients was estimated to be 130, taking into consideration an 8% withdrawal. The characteristics of the patients, toxicity and tumour response rates between the treatment groups were compared with the χ^2 test of homogeneity of Fisher's exact test as appropriate on full or collapsed tables using a BMDP statistical package [25]. A two-tailed non-paired *t*-test was used to compare dose intensity between the two treatment groups [26]. Survival and ttp were calculated using the Kaplan–Meier method [27]. The crude relationships of treatment or other patients' characteristics to ttp and survival were analysed using the log-rank [28], Breslow [29] and Tarone-Ware [30] tests. The proportional hazards model, as proposed by Cox [31], was used to analyse ttp and survival while adjusting simultaneously for various prognostic factors. Finally, multivariate logistic regression analysis was used to examine the influence of treatment and various prognostic factors on tumour response [32]. All patients included in the present study were analysed on the intention to treat basis.

RESULTS

Patients

Between August 1987 and September 1991, 130 patients with stage IIc, III and IV ovarian cancer entered the study. The selected patients in each participating hospital were randomly assigned to treatment CB or CB-EC. Randomisation procedure was performed by sealed envelops in each centre. The characteristics of the patients are shown in Table 1. More patients were entered into the monotherapy arm as a result of an administrative error in the randomisation procedure which was due to an inappropriate sequence of the content of the sealed envelops. There were no statistically significant differences in the distribution of characteristics of the patients (performance status, tumour stage, histology, histological grade, initial surgery, creatinine clearance) between the two chemotherapy groups (Table 1). Total hysterectomy and bilateral adnexectomy with omentectomy and thorough abdominal exploration was performed in 29 (40%) patients in the monotherapy group and 19 (33.3%) in the combination group. Other major debulking operations were performed in 18 patients in each group. In 14 cases, the surgeon could not reliably quantify the extent of the bulky residual disease for reasons such as frozen pelvis, multiple peritoneal seedings and retroperitoneal disease.

Up to September 1994, the median duration of follow-up was 28.5 months (range 2.3–85.2). 5 patients, 4 in the CB and 1 in the CB-EC group, were lost to follow-up 3–36 months after randomisation.

Treatment

Treatment was interrupted after one to five cycles in 3 patients in the monotherapy group and in 6 of the combination group, as a result of disease progression before the end of therapy; refusal or other reasons accounted for a further 10 patients. After the end of the six courses of protocol treatment, 4 other patients in the monotherapy group were treated for an additional one to four cycles, the physician in charge having reached this decision in these cases because the patients did not wish to undergo second-look surgical evaluation. DI, duration of the cycles and treatment delays are shown in Table 2. There was no significant difference in the RDI between the two treatment groups.

Toxicity

The incidence of adverse reactions is shown in Table 3. The differences between groups were significant ($P < 0.05$) with regard to nausea and vomiting (most patients with CB-EC having grade 2 toxicity) and to alopecia. 11 of the 13 patients with severe nausea and vomiting in the first course had less than two emetic episodes and reported absent or mild nausea in the following cycles, where the alternative prophylaxis with dexamethasone and ondansetron was used.

Additionally, anaemia necessitating transfusions (haemoglobin <10 gm/dl) was observed in approximately 20% in the CB and 23% in the CB-EC group of patients. 4 cases of febrile neutropenia were observed, 3 in the CB-EC group; 1 patient in the CB group showed elevated liver enzymes.

Tumour response, second-look surgery

The response to treatment is indicated in Table 4. 6 patients in the monotherapy group and 1 in the combination group were not deemed evaluable for response due to the patients' refusal to continue treatment until assessment. There were 40 cCRs (54%) and 12 cPRs (16.4%) in the CB group and 33 cCRs (57.8%) and 8 cPRs (14%) in the CB-EC group. There were no statistically significant differences between the response in the two groups.

The RDI (less or more than 0.8 of planned dose) was correlated positively with pathologically confirmed complete remission, in the CB arm only ($P = 0.03$), while test power was insufficient for a statement concerning the CB-EC group.

Logistic regression analysis of response with the treatment group (CB versus CB-EC), size of residual disease (0 versus ≤2 versus >2 cm), grade of the tumour (1 and 2 versus 3 and 4) and stage of disease (III versus IV) showed that the size of the residual disease was the only significant variable ($P = 0.0189$).

Of the 73 patients with a clinical CR, 38 (17 in CB, 21 in the CB-EC arm) were re-evaluated surgically at the end of treatment. CR was confirmed in 24 (63%) of these patients, 11 (65%) in the CB and 13 (62%) in the CB-EC arm; these differences were not statistically significant. 11 additional patients in the CB and 13 in the CB-EC group, who were judged clinically to have PR or SD were operated for further

Table 1. Patients' characteristics

	Total	(%)	CB	(%)	CB-EC	(%)	*P* value
Number	130		73		57		
Age (years)							
Range	30–78		40–78		30–71		
Median	60		62		60		
Creatinine clearance (ml/min)							
Median			65		70		0.3386*
Range			(54–120)		(51–118)		
Performance status (WHO)							
0–1	91	(70.0)	51	(69.9)	40	(70.2)	
2	32	(24.6)	20	(27.4)	12	(21.1)	0.2609*
3	7	(5.4)	2	(2.7)	5	(8.8)	
Tumour stage (FIGO)							
IIc	5	(3.8)	2	(2.7)	3	(5.3)	
IIIa	12	(9.2)	6	(8.2)	6	(10.5)	
IIIb	12	(9.2)	11	(15.1)	1	(1.8)	0.0950*
IIIc	79	(60.8)	44	(60.3)	35	(61.4)	
IV	22	(16.9)	10	(13.7)	12	(21.1)	
Histology							
Serous	93	(71.5)	54	(74.0)	39	(68.4)	
Mucinous	15	(11.5)	7	(9.6)	8	(14.0)	
Endometrioid	11	(8.5)	6	(8.2)	5	(8.8)	0.1472†
Clear-cell	3	(2.3)	3	(4.1)	0	(0)	
Mixed	2	(1.5)	0	(0)	2	(3.5)	
Undifferentiated	4	(3.1)	2	(2.7)	2	(3.5)	
Unclassified	2	(1.5)	1	(1.4)	1	(1.8)	
Initial surgery							
Extensive debulking	84	(64.6)	47	(64.4)	37	(64.9)	0.9522*
Residual disease							
None	16	(12.3)	7	(9.6)	9	(15.8)	
Diameter							
<2 cm	45	(34.6)	28	(38.4)	17	(29.8)	
2–5 cm	18	(13.8)	11	(15.1)	7	(12.3)	0.6982*
>5 cm	37	(28.5)	19	(26.0)	18	(31.6)	
Non-defined	14	(10.8)	8	(11.0)	6	(10.5)	
Grade							
1	11	(8.5)	7	(9.6)	4	(7.0)	
2	44	(33.8)	28	(38.4)	16	(28.1)	
3	51	(39.2)	27	(37.0)	24	(42.1)	0.6421*
4	9	(6.9)	4	(5.5)	5	(8.8)	
Unclassified	15	(11.5)	7	(9.6)	8	(14.0)	

CB, carboplatin; CB-EC, carboplatin/epirubicin/cyclophosphamide. * No statistically significant differences (χ^2 test of homogeneity). † No statistically significant differences (based on collapsed tables).

*Table 2. Treatment intensity**

Chemotherapy group	Planned dose (mg/m²/week)	Dose given (mg/m²/week) Median	Dose intensity (mg/m²/week) Range	Mean relative dose intensity		Average cycle duration per patient (days) Range	Mean	Average delay per patient per course Up to 7 days	>7 days
Carboplatin (CB)	133.33	106.5	(81.4–133.3)	0.8209		21–37	25.5	67%	13%
Carboplatin/	100	83.6	(46.0–113.2)	0.8469					
epirubicin/	16.66	14.2	(7.5–17.8)	0.8467	0.8406	20–34	24.5	51%	11%
cyclophosphamide (CB-EC)	166.66	140.0	(69.0–178.0)	0.8283					

*No statistically significant differences (Student's *t*-test *P* value = 0.48).

Table 3. Toxicity as percentages of patient numbers (%)

	Chemotherapy group							
	CB				CB–EC			
WHO grade	0	1	2	3–4	0	1	2	3–4
WBC	34.5	30	30	5.5	26.0	35	32	7
Platelets	88.6	7	3	1.4	98.0	0	2	0
Haemoglobin	49.3	31.5	19.2	—	45.6	31.6	22.8	—
Creatinine elevation	97.0	3	0	0	98.0	2	0	0
Nausea/vomiting* ($P = 0.014$)	13.0	47	32	8	0.0	28	60	12
Neurological	96.0	4	0	0	98.0	2	0	0
Hair loss* ($P < 0.001$)	73.0	25	1.4	—	14.0	54	42	—
Skin	0.0	0	0	0	96.0	4	0	0

CB, carboplatin; CB-EC, carboplatin/epirubicin/cyclophosphamide. *Statistically significant ($P < 0.05$) tested by means of χ^2 test or homogenity or Fisher's exact test on full or collapsed tables.

Table 4. Tumour response

	Chemotherapy group		
	CB (%)	CB-EC (%)	*P* value*
Clinical response	73	57	
Complete	40 (54.8)	33 (57.8)	
95% confidence intervals	(40–64)	(44–71)	0.2082
Partial	12 (16.4)	8 (14.0)	
Stable disease	9 (12.3)	7 (12.3)	
Progressive	6 (8.2)	8 (14.0)	
Non-evaluable	6 (8.2)	1 (1.8)	
Second-look evaluation			
Number operated in clinical CR	17	21	
Pathology confirmed CR	11 (64.7)	13 (61.9)	0.8494

CB, carboplatin; CB-EC, carboplatin/epirubicin/cyclophosphamide. *No statistically significant differences based on χ^2 test of homogeneity.

debulking. In 4 of these patients, the surgeon documented a progression of the disease.

Time to progression

Median ttp was 16.89 months (0.82–76.33) with no significant differences between the two treatment groups (Figure 1). The impact of selected variables on ttp was assessed with univariate analysis using the Kaplan–Meier method. These variables were treatment regimen (CB versus CB-EC), size of residual disease (0 versus ≤2 versus >2 cm), tumour grade (1 and 2 versus 3 and 4), stage of disease (III versus IV) and PS (0 and 1 versus 2 and 3). Results are shown in Table 5. In a multivariate stepwise Cox analysis with all the above variables only PS maintained its significance as a prognostic factor, with a negative impact on ttp (Figure 2). The hazard odds for PS 2 and 3 versus 0 and 1 was 1.57.

A separate analysis was also performed to assess the impact of pCR on ttp. Median ttp for the 24 patients with histologically confirmed CR was 46.85 months as compared to 15.7 months in patients with clinical CR who had evidence of disease at second-look laparotomy. These differences were highly significant ($P < 0.001$). Finally, patients with cCR had significantly longer ttp than those with PR or SD (22.9 versus 10.5 versus 6.3 months, respectively; $P < 0.001$).

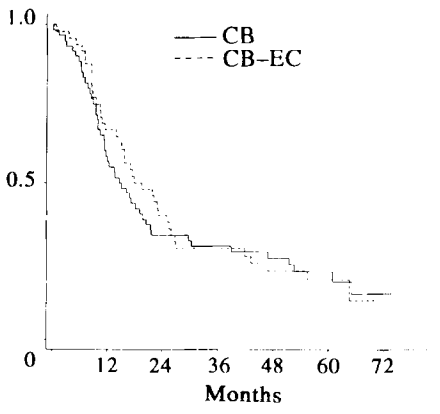

Figure 1. Time to progression according to chemotherapy group. $P = 0.5884$ (NS*).

Survival

Up to September 1994, 26 (20%) patients were still alive, 17 (23%) in the CB and 9 (16%) in the CB-EC group. Median survival for all patients was 29.54 months (2.26–85.18) with no significant differences between the two treatment groups (Figure 3). Of the 73 patients who achieved a cCR, 54 (74%) relapsed, 29/40 (73%) in the CB and 25/33 (76%) in the CB-EC group. The difference between these proportions was not significant. Median survival of patients with cCR was 47.7 months and of those with PR 19.4 months. Patients with SD had 13.3 months median survival while those with PD only 8.2 months. These differences were highly significant ($P < 0.001$). The impact of selected variables on survival was assessed with an univariate analysis using the Kaplan–Meier method. These variables were again treatment regimen, size of the residual disease, tumour grade, stage of the disease and PS. Results are shown in Table 5. Multivariate stepwise Cox analysis with the above variables showed stage and PS to be the only important prognostic factors with a negative impact on survival. The hazard odds for stage IV versus stage III was 2.66 while for PS 2 and 3 versus 0 and 1 it was 1.70 (Figures 4 and 5).

Median DFS was 22.89 months (0.16–76.2), 21.57 months (0.16–76.2) for the CB group and 24.92 months (0.82–74.75) for the CB-EC group. This difference was not statistically significant. A separate analysis was also performed to assess the impact of the chemotherapy (CB versus CB-EC) on ttp, RFS, DFS and overall survival, according to the initial residual disease (0 versus 2 versus >2 cm). No statistically differences were found between the two treatment groups (Table 6).

DISCUSSION

Until recently, cisplatin monotherapy or its combination with other drugs, including an alkylating agent, have been accepted by most clinicians as the standard chemotherapy for patients with AEOC [33, 34]. Well-designed prospective randomised trials show that CBDCA combinations can safely and effectively replace its parent compound in these patients [35, 36].

The relatively high CR and PR rates observed in both arms of our study are comparable to those reported for cisplatin and CBDCA or their combinations and confirm the efficacy of CBDCA-based chemotherapy [37, 38].

At the 5% level, our study did not detect a superiority in response rate, ttp or survival of the combination with epirub-

Table 5. The impact of selected variables on time to progression (ttp) and survival — univariate analysis

	Median ttp (months)	Median survival (months)
Treatment (CB versus CB-EC)	14.6 versus 17.9 (NS)	28.3 versus 29.5 (NS)
Residual disease (0 versus < 2 versus > 2 cm)	43.2 versus 17.9 versus 12.4 ($P = 0.0361$)	68 versus 29.5 versus 21.9 ($P = 0.0031$)
Tumour grade (1 and 2 versus 3 and 4)	17 versus 18.2 (NS)	32.4 versus 31.8 (NS)
Stage of disease (III versus IV)	16.9 versus 15.2 ($P = 0.0493$)	32.4 versus 14.6 ($P = 0.003$)
Performance status (0 and 1 versus 2 and 3)	19.5 versus 11.4 ($P = 0.0232$)	34.2 versus 16.1 ($P = 0.0088$)

CB, carboplatin; CB-EC, carboplatin/epirubicin/cyclophosphamide. NS, not significant

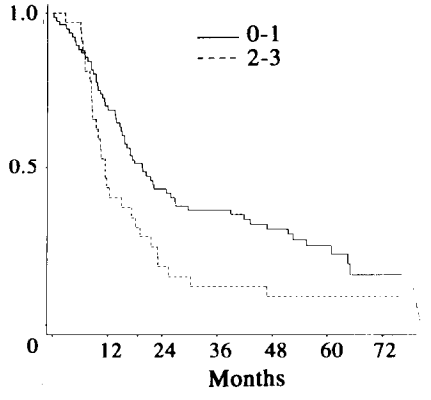

Figure 2. Time to progression according to performance status. $P = 0.0232$.

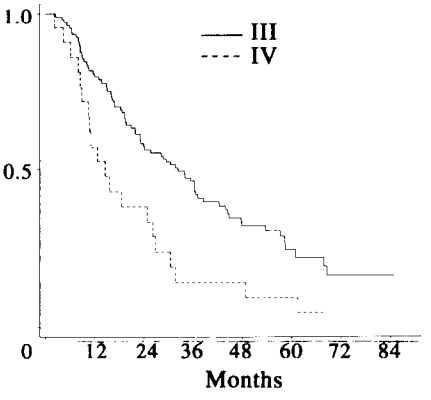

Figure 4. Survival according to stage of disease. $P = 0.0030$.

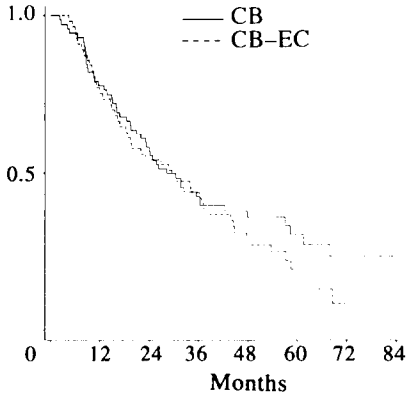

Figure 3. Survival according to chemotherapy group. $P = 0.5788$ (NS*).

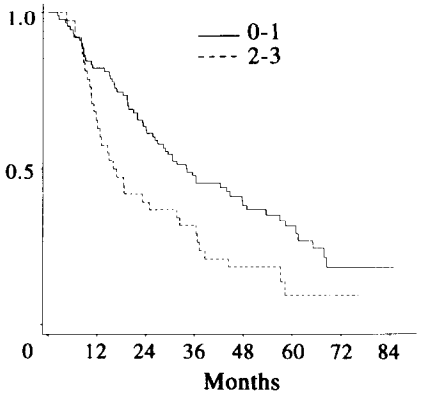

Figure 5. Survival according to performance status. $P = 0.008$.

icin and cyclophosphamide. However, it should be emphasised that the size of the present study was inadequate to draw any definitive conclusions. Moreover, the 50 mg/m^2 dose of epirubicin, used in our study, was rather low compared to the administered doses of doxorubicin in other trials. Nevertheless, results of randomised trials, where cisplatin/ cyclophosphamide were compared with cisplatin/cyclophosphamide/doxorubicin did not show any significant survival difference [5, 11]. However, in a recent meta-analysis study of 1194 patients with advanced ovarian cancer, a statistically significant benefit in frequency of negative second-look laparotomies and survival (6% survival benefit at 3 years) was found in the group of patients which was treated with the three-drug combination [39].

Our data also confirmed the prognostic role of the size of the residual tumour following initial surgery. It was clear that patients with lower tumour burden survived significantly longer and this is in agreement with the results of other studies [8, 40, 41]. Moreover, patients with histologically confirmed CRs showed a significantly higher median survival compared to those who had clinical but not pathological CR. This is explained by the fact that a proportion of patients without clinical evidence of disease still have residual tumour at the time of second-look surgery [42, 43]. In our study of 38 patients with clinical CR who had second-look surgery, only 24 (63%) were found without evidence of disease. Despite the limitations of the clincial assessment of response, this is still a valuable prognostic factor for survival as has been confirmed in previous studies [42]. This was also the case in the present study. Among other factors already reported as significant, FIGO stage was also confirmed in the present study [33].

Table 6. The impact of chemotherapy on time to progression (ttp), relapse-free survival (RFS), disease-free survival (DFS) and overall survival according to the initial residual disease

Initial residual disease	Regimen	Median ttp (months) No. patients	Median ttp (months) Median time	Median ttp (months) P value	Median RFS (months) No. patients	Median RFS (months) Median time	Median RFS (months) P value	Median DFS (months) No. patients	Median DFS (months) Median time	Median DFS (months) P value	Median survival (months) No. patients	Median survival (months) Median time	Median survival (months) P value
0 cm	CB	7	64.95 (9.54–74.85)	0.56*	7	64.95 (9.54–74.85)	0.56*	7	64.95 (9.54–75.85)	0.56*	7	67.97 (30.52–74.85)	0.71
	CB-EC	9	43.21 (8.46–74.81)		9	43.21 (8.46–74.8)		9	43.21 (8.46–74.8)		9	65.25 (19.84–74.75)	
≤2 cm	CB	22	13.74 (0.16–76.20)	0.97*	19	19.08 (0.16–76.20)	0.89*	18	19.08 (0.16–76.20)	0.99*	28	28.26 (2.59–85.18)	0.50*
	CB-EC	16	17.87 (5.08–66.82)		14	19.48 (6.26–66.82)		12	19.48 (8.36–66.82)		17	29.54 (6.10–66.82)	
>2 cm	CB	26	11.44 (2.85–76.33)	0.19*	20	11.74 (6.10–64.10)	0.12*	9	15.18 (7.64–64.10)	0.34*	30	21.93 (2.26–76.33)	0.60*
	CB-EC	18	15.70 (6.98–64.56)		14	15.70 (6.98–64.56)		8	17.38 (10.92–64.56)		25	19.38 (4.49–68.95)	

CB, carboplatin; CB-EC, carboplatin/epirubicin/cyclophosphamide. *Not statistically significant.

Thus, median survival of patients with stage III was 32.4 months compared to that of stage IV which was only 14.6 months. Finally, the observation that patients with good PS lived longer was also confirmed in our study [44–46]. Patients with good PS (0 or 1) had a median survival of 34.2 months compared to those with poor PS (2 or 3) who lived only 16.1 months.

The multivariate analysis identified stage and PS to be the most important independent prognostic factors for survival. This is in accordance with other reports where the above two variables as well as the size of residual disease and the presence of ascites were found to influence survival significantly [44–47]. The reason why we identified only two of these variables to be significant is unclear, although this is probably a reflection of the reduced power of our study because of its small size.

The main toxicity was, as expected, haematological. Thrombocytopenia, mostly mild, was seen almost exclusively in the monotherapy arm. The acceptable non-haematological toxicity of carboplatin when administered either alone at a dose of 400 mg/m^2 or in the CB-EC combination at a dose of 300 mg/m^2 is in agreement with previous studies [12,48]. Neurotoxicity and nephrotoxicity were mild and infrequent. Nausea and vomiting were more pronounced in the combination arm. Intractable nausea and vomiting in the first course was managed in most cases by changing from metoclopramide to dexamethasone and ondansetron. As expected, hair loss was more severe in the combination arm. No death related to treatment toxicity was observed.

Although most investigators have administered the drug as monotherapy or in combination at a dose of 400 mg/m^2 every 4 weeks [12, 15, 37, 38, 48], we decided to shorten the intervals by giving it every 3 weeks. However, the fact that two thirds of our patients required some delay indicates that the more intensive schedule is not generally feasible without the use of haemopoetic growth factors, which might allow the administration of higher doses [12]. Moreover, the dose of CBDCA was estimated on a mg/m^2 basis. It is possible that if the dose of CBDCA was calculated according to the area under the concentration times time curve (AUC), the incidence of serious myelotoxicity might have been different [49].

In the monotherapy arm, the administration of relative dose intensity higher than 0.8 of that planned by the protocol was positively correlated with the rate of surgically confirmed CR. This is in agreement with previous reports on dose intensity and response [13, 50, 51].

In conclusion, the efficacy of carboplatin, either as a single agent or in combination, is confirmed once more in our patients with AEOC, with acceptable toxicity. The combination of carboplatin/cyclophosphamide/epirubicin used in this study does not substantially improve response rates or survival. Additional comparative trials are necessary to study the respective roles of dose and treatment schedule of carboplatin.

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