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Clinical study

Cyclophosphamide, epirubicin and cisplatin (CEP) versus epirubicin plus cisplatin (EP) in stage Ic–IV ovarian cancer: a randomized phase III trial of the Gynecologic Oncology Group of the Comprehensive Cancer Center Limburg

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Cisplatin is the most important drug in the treatment of advanced ovarian cancer. The role of anthracyclines is controversial. We compared a combination of epirubicin plus cisplatin (EP) with a regimen of cyclophosphamide, epirubicin and cisplatin (CEP). Patients with stage Ic–IV ovarian cancer were randomized to receive either epirubicin 100 mg/m^2 plus cisplatin 75 mg/m^2 q 4 weeks or cyclophosphamide 500 mg/m^2 plus epirubicin 75 mg/m^2 plus cisplatin 50 mg/m^2 q 4 weeks, which we considered the reference treatment based on our previous experience. Patients were initially debulked, followed by six cycles of chemotherapy, or in case primary debulking was insufficient or considered inappropriate, secondary debulking was attempted in selected cases after sufficient chemotherapy-induced regression. Optimal debulking was defined as residual lesions ≤2 cm. A total of 210 patients (191 eligible) were randomized. Results did not show significant differences in all major endpoints (pathologically documented complete response and survival). The median survival for all patients was 34 months, for patients with stage III 26 months, for patients with stage IV 20 months and it has not been reached for patients with stage Ic–II. As no significant differences between an equitoxic regimen of EP and CEP were detected, it might be more useful to look again at the anthracyclines as part of combination chemotherapy instead of the alkylating agents. [© 1999 Lippincott Williams & Wilkins.]

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Introduction

There can be little doubt that the most important drug in the treatment of advanced ovarian cancer is cisplatin. The addition of other agents such as alkylating drugs or anthracyclines may improve results but there exists no firm consensus concerning the most optimal combination. In particular, the role of the anthracyclines has remained controversial although two meta-analyses suggested benefit on histologically complete response rate (HCR) and long-term survival.[1,2]

In previous phase II trials, our Group has treated over 200 patients with the CAP (cyclophosphamide, adriamycin and cisplatin) and CEP (cyclophosphamide, epirubicin and cisplatin) regimen with equivalent results.[3,4] In those studies we utilized cyclophosphamide at a dose of 500 mg/m^2 and cisplatin at a dose of 50 mg/m^2 on a 4 weekly basis which results in a substantially lower dose intensity of cyclophosphamide and cisplatin as utilized in the CP regimen (cyclophosphamide 750 mg/m^2 and cisplatin 75 mg/m^2 q 3 weeks) which at that time was considered by many clinicians the more optimal treatment. We felt that the inclusion of an anthracycline might contribute to the treatment outcome

and therefore we embarked in 1988 on a randomized trial comparing the CEP and EP regimens. The aim of the study was to assess the activity of a regimen of two active agents in an equitoxic dose compared with our 'standard' three-drug CEP regimen.

Patients and methods

Eligibility criteria included histologically proven epithelial ovarian cancer, FIGO stage Ic–IV disease, WHO performance status 0–2, adequate organ functions, no previous chemo- or radiotherapy, age <76 years and informed consent. Primary surgery had to be attempted with the intent to debulk to lesions ≤2.0 cm. In case primary adequate surgery was impossible, patients received primary chemotherapy and secondary surgery had to be attempted after sufficient chemotherapy induced regression of the tumor. In the case of primary optimal surgery a second-look procedure was advised after six cycles in the case of clinically complete remission. Second-look was, however, not mandatory, because at that time this procedure was controversial. In case a second-look was performed, treatment was discontinued in case of a HCR. In case of stable disease (SD), partial response (PR) or histologically minimal disease (HMD), treatment was continued with three more cycles. In cases of secondary surgery, chemotherapy was continued to a maximum of nine cycles.

Chemotherapy consisted of CEP (cyclophosphamide, 500 mg/m^2, epirubicin, 75 mg/m^2 and cisplatin, 50 mg/m^2) or EP (epirubicin, 100 mg/m^2 and cisplatin, 75 mg/m^2), i.v., q 4 weeks.

Randomization was done by telephone calls to the data center of the Comprehensive Cancer Center Limburg.

In order to demonstrate a relative increase in the median survival with 50% a total of 192 evaluable patients had to be randomized (α=0.05, β=0.20, two-tailed test). Toxicity and response were compared by the χ^2 test. Time to progression and survival was estimated by the Kaplan-Meier method. Differences between the curves were tested for statistical significance by the log-rank test. Death or progression were chosen as different endpoints. To investigate the effects of other variables on survival or progression, Cox's proportional hazards model was used. The analysis was performed using the PHREG procedure of SAS.[5] In the comprehensive model, chemotherapy, stage (four categories), optimal debulking surgery and performance status (two categories) were entered as explanatory variables. The variables for performance status were removed from the model because the p values of the parameter estimates were not significant and the removal of these variables did not influence the parameter estimates of the remaining variables in the model. Log(-log) survival curves were inspected to check the proportional hazards assumption essential to Cox's proportional model.

Results

Between 1988 and 1995 a total of 210 patients were randomized. Nineteen patients were not eligible because of wrong histology (4), second malignancy (5), inadequate organ function (1), refusal (1), lost to follow-up (2) or performance status (6), leaving a total of 191 eligible patients. Patient and tumor characteristics were balanced with the exception of extent of surgery. There were more patients with stage III and no residual lesions after surgery in the EP arm (Table 1).

Toxicity

There was marginal significantly more hematologic toxicity in CEP mainly due to leucopenia (p= 0.063) (Table 2). Other toxicities were as expected and included alopecia, nausea/vomiting, mucositis, neuropathy and cardiomyopathy, without significant differences (Table 3). The median number of courses was 6 (median 1–10). In 15 patients treated with CEP and in 16 treated with EP, one or more courses were delayed.

Table 1. Patient characteristics

	CEP (n=94)	EP (n=97)
Stage Ic–II	18	21
Stage III (no residual disease)	7	14
disease ≤2 cm	18	20
residual >2 cm	36	30
Stage IV	15	12

Table 2. Hematologic toxicity

	CEP	EP
Hematologic toxicity grade 4 (leucopenia and/or thrombopenia grade 4)	29%	19%
Anemia grade 3–4	5%	6%
Leucopenia grade 4	27%	16%
Thrombopenia grade 3–4	11%	13%

P=0.063.

The dose intensity was well maintained as approximately 90% of anticipated dose was administered in both arms (Table 4).

Response

There were no significant differences in the response (Table 5). The higher HCR rate in EP could be explained by the higher number of patients with stage III without macroscopic residual disease after surgery.

Time to progression and survival

Neither the time to progression nor the survival curves were significantly different either overall or in subgroups (Figures 1 and 2). The median time to progression for all patients was shorter in CEP, 15 months, whereas it was 23 months in patients treated with EP (log-rank; p=0.13). Median survival for all patients was 25 months in CEP and 37 months in EP but according to the log-rank test this difference was not significant (Table 6). Survival was significantly influenced by the stage of the disease. Median survival has not been reached in patients with stage Ic-II. It was 26 months in patients with stage III and 20 months in patients with stage IV (log-rank; p=0.03) without significant differences between the treatment arms. The other most important prognostic factor for patients with stage III-IV was the fact whether or not optimal debulking was possible. Median follow-up was 5 years and 100 of 191 patients died within that period.

Second-line treatment upon relapse was not defined in our trial but most patients received combinations of carboplatin and/or paclitaxel, and it does not appear likely that the lack of a significant survival difference could be due to different second-line treatment.

Multivariate analysis

In the multivariate analysis of survival and time to progression chemotherapy did not influence outcome significantly. The hazard ratio, after adjustment for other possible confounding factors such as stage and surgery, of EP versus CEP was 0.96 (95% confidence intervals 0.65-1.43) for overall survival and 0.84 (95% confidence intervals 0.58-1.20) for time to progression.

Discussion

This prospective, randomized, multicenter study in chemo-naive patients with advanced ovarian cancer

Table 3. Non-hematological toxicity

	CEP	EP
Nausea/vomiting grade 3–4	18%	27%
Neurotoxicity grade 3–4	0%	3%
Mucositis grade 3–4	3%	2%
Cardiotoxicity grade 3–4	3%	0%
Creatinine grade 3–4	0%	3%

Table 5. Response

	CEP (n=94)	EP (n=97)
HCR	11	17
HMD	5	9
CCR	35	44
PR	21	16
SD	3	2
PD	16	6
NE	3	3
HCR rate[a] (p=0.094)	11/56 (20%)	17/50 (34%)

[a]In the denominator patients with CCR are excluded as well as patients declared NE (not evaluable) for response.

Table 4. Total dose administered after three and six courses

Drugs	Courses	CEP			EP		
		Anticipated (mg/m^2)	Administered (mg/m^2)	%	Anticipated (mg/m^2)	Administered (mg/m^2)	%
Epirubicin	3	225	221	98	300	286	95
	6	450	410	91	600	532	89
Cyclophosphamide	3	1500	1447	96			
	6	3000	2684	89			
Cisplatin	3	150	148	99	225	216	96
	6	300	276	92	450	402	89

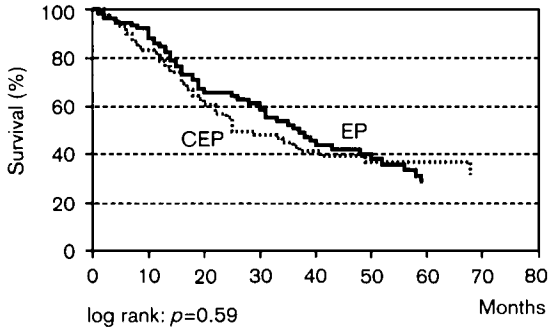

Figure 1. Survival curves for CEP versus EP for all patients.

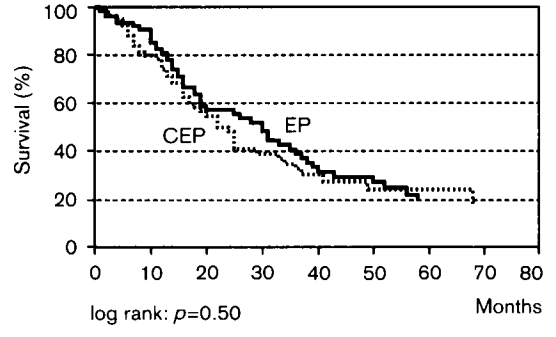

Figure 2. Survival curves for CEP versus EP for patients with stage III–IV disease.

Table 6. TTP and survival in all patients

Median TTP CEP	15 months
Median TTP EP	23 months (log-rank; p=0.13)
Median survival CEP	25 months
Median survival EP	37 months (log-rank; p=0.58)

TTP, time to progression.

Table 7. Survival according to randomization, stage and debulking (only stage III–IV)

Median TTP CEP	13 months
Median TTP EP	16 months
(p=0.10; hazard ratio EP versus CEP in multivariate analysis 0.81)	
Median survival CEP	22 months
Median survival EP	30 months
(p=NS; hazard ratio EP versus CEP in multivariate analysis 0.96)	
Median survival ODS	33 months
Median survival NODS	19 months
(p=0.001; hazard ratio NODS versus ODS in multivariate analysis 1.91; CI: 1.25–2.92)	
Median survival stage III	26 months
Median survival stage IV	20 months
(p=0.02; hazard ratio in multivariate analysis stage IV versus III 1.61; CI: 0.95–2.74)	

ODS: optimal debulking surgery; residual lesions $\leq$2 cm.
NODS: non-optimal debulking surgery; residual lesions >2 cm.

was performed to investigate whether or not, at equitoxic doses, EP was superior to CEP in terms of response rate and survival. The rationale was supported by the results of two meta-analyses[1,2] in the early 1990s, suggesting that the combination of cisplatin and an anthracycline should be the backbone of the treatment of advanced ovarian cancer due to improved HCR rate and long-term survival.

Although the study has not revealed significant differences between EP and CEP in the major endpoints, the possibility that EP is superior to CEP at the studied doses can not totally be ruled out. In that case, however, the improvement in median survival will probably be well below 50% as was anticipated in the hypothesis on which the number of patients was based.

Because it is generally accepted that cisplatin in combination regimens should be given in a dose-intensity of 25 mg/m^2/week (75 mg/m^2, every 3 weeks), it could be argued that the outcome of EP might have resulted from a more optimal dose of cisplatin. However, as has been pointed out, results of prospective, clinical, dose-finding studies of cisplatin as a single agent or in combination regimens are conflicting. In one study initially showing improved outcome when higher dose therapy was used, the apparent benefit of the high dose disappeared as data matured.[6] Furthermore, hematologic toxicity, although intended to be the same in our study, was higher with CEP, therefore underdosing of CEP appears unlikely. Finally, results of our previous phase II studies with CAP and CEP, in which we applied the same dose of cisplatin as in the current study, showed activity in accordance with the literature and very low neurotoxicity.[3,4]

It could also be argued that higher doses in EP might have been possible with potential superior results. In particular, the maximum tolerated dose of epirubicin in addition to an adequate dose of cisplatin has not been assessed in patients with advanced ovarian cancer. It appears unlikely, however, that a dose of 100 mg/m^2 of epirubicin q 4 weeks (dose intensity 25 mg/m^2/week) can be considered as suboptimal in combination regimens. Epirubicin, 150 mg/m^2 q 3 weeks (dose intensity 50 mg/m^2/week), has been assessed as a single agent in second-line treatment

(after previous cisplatin-containing combination therapy) and resulted in a response rate of 20% in 105 patients. Toxicity, however, was considerable with 56% WHO grade 4 leucopenia with serious infections in 7% of the patients.[7]

Cyclophosphamide dose intensity has consistently been shown to be irrelevant and in the past, when alkylating agents were utilized as single agents in ovarian cancer, a survival benefit has never been obtained. Our results appear to confirm that epirubicin has significant activity in advanced ovarian cancer and it might be more useful to look again at the anthracyclines as part of combination chemotherapy instead of the alkylating agents.

During recent years much interest has been given to paclitaxel, because one large trial conducted by the Gynecologic Oncology Group in the US showed a significant higher complete clinical response rate and significant improved progression-free survival and overall survival of paclitaxel plus cisplatin compared with cyclophosphamide plus cisplatin in women with incompletely resected stage III and IV ovarian cancer.[8] A second large study comparing the same chemotherapy regimens and including 680 patients was carried out by a collaboration of four European and Canadian cooperative groups, and has recently completed accrual. The first data presented in abstract form appear to confirm the superiority of paclitaxel plus cisplatin to the combination of cyclophosphamide and cisplatin in advanced ovarian cancer.[9]

Docetaxel 100 mg/m^2 over 1 h has been studied in a phase II setting in ovarian cancer patients after one or two prior platinum regimens and found to have activity similar to paclitaxel (response rate overall 26% in 99 assessable patients).[10,11] Based on the results of our study a possible further improvement might come from the addition of epirubicin to a combination of cisplatin and a taxane.

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