EUROPEAN JOURNAL OF CANCER 44 (2008) 2169–2177

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Carboplatin and Paclitaxel *versus* Cisplatin, Paclitaxel and Doxorubicin for first-line chemotherapy of Advanced Ovarian Cancer: A Hellenic Cooperative Oncology Group (HeCOG) study

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ARTICLE INFO

Article history:
Received 24 April 2008
Received in revised form
11 June 2008
Accepted 16 June 2008
Available online 6 August 2008

Keywords:
Advanced
Anthracycline
Carboplatin
Cisplatin
Chemotherapy
Doxorubicin

ABSTRACT

Introduction: The combination of Carboplatin and Paclitaxel is considered the standard of care as initial chemotherapy for Advanced Ovarian Cancer (AOC). We compared this regimen with the combination of Cisplatin, Paclitaxel and Doxorubicin.

Patients and methods: Patients with AOC were randomised to either six courses of Paclitaxel 175 mg/m^2 plus Carboplatin 7AUC or Paclitaxel at the same dose plus Cisplatin 75 mg/m^2 plus Doxorubicin 40 mg/m^2.

Results: Analysis was performed on 451 patients. The treatment groups were well balanced with regard to patient and disease characteristics. Performance status (PS) was better in the anthracycline arm. In terms of severe toxicity, the only significant difference between the two groups was the development of febrile neutropaenia in the anthracycline arm. Overall response rate was similar in both groups. With a median follow-up of 57.5 months, a marginal significance towards improved Progression-Free Survival (PFS) was noted in favour of the anthracycline arm, whilst there was no difference in overall survival. In multivariate

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.06.035

First line
Initial
Ovarian cancer
Paclitaxel

analysis the hazard of disease progression at any time was significantly decreased by 25.5% for patients of the anthracycline arm.

Conclusion: The combination of Cisplatin, Paclitaxel and Doxorubicin demonstrates a marginal PFS improvement, but no additional survival benefit when compared with the standard Carboplatin/Paclitaxel regimen.

1. Introduction

The combination of platinum with a taxane is considered the standard of care for advanced epithelial ovarian cancer. Over the last decade, a number of well-designed studies have demonstrated its superiority over other regimens. In the GOG Protocol 111, Cisplatin at 75 mg/m^2 was combined with either Paclitaxel at 135 mg/m^2 as a 24-h infusion or Cyclophosphamide at 750 mg/m^2. The comparison favoured the Paclitaxel arm[1] in terms of clinical response, progression-free survival and median survival. With a follow-up of over 60 months, a 28% reduction in the risk of progression and a 34% reduction in risk of death were noted amongst those patients treated with Cisplatin/Paclitaxel as compared to Cisplatin/Cyclophosphamide.[2] Validation of these results became available from a large collaborative trial conducted in Europe and Canada. In this study, Paclitaxel was administered at 175 mg/m^2 over 3 h. The Paclitaxel – based arm was associated with improved response, progression – free survival and overall survival.[3] Other studies have indicated that the combination of Carboplatin and Paclitaxel is feasible and highly effective in ovarian cancer patients.[4] Three large randomised trials, which compared Cisplatin plus Paclitaxel *versus* Carboplatin plus Paclitaxel, did not show any differences in response rates, progression-free survival and overall survival between the two arms. Apart from demonstrating a better toxicity profile, the combination of Carboplatin with Paclitaxel had one more advantage: it made outpatient administration of chemotherapy feasible [5–7] for this group of patients. Therefore, the new combination became firmly established as the standard of care in first-line chemotherapy for advanced epithelial ovarian cancer. As expected it has extensively been used as the control arm for investigational trials over the past decade.[8]

The anthracyclines have demonstrated single-agent activity in platinum-pre-treated ovarian cancer[9] Two meta-analyses have shown a survival benefit for platinum/anthracycline-based combinations when compared with platinum-based combinations without anthracyclines.[10,11] A' Hern and Gore examined the impact of the addition of Doxorubicin to ovarian cancer regimens by performing an overview of data from meta-analyses. They concluded that the addition of Doxorubicin significantly improved survival.[12] These data have generated a significant interest in assessing the role of taxane/platinum/anthracycline combination in advanced epithelial cancer. Hill et al. reported preliminary results of a combination consisting of Cisplatin 75 mg/m^2, Paclitaxel 175 mg/m^2 over 3 h and Doxorubicin 50 mg/m^2 IV bolus every three weeks; G-CSF was used when neutrophils reached nadir. The regimen appeared active but also toxic.[13]

A similar study was reported by the GOG in which Paclitaxel 135 mg/m^2 IV over 24 h and Cisplatin 75 mg/m^2 were combined with escalating doses of Doxorubicin starting from 30 mg/m^2 with G-CSF support. Dose limiting toxicity was reached at the 40 mg/m^2 dose of Doxorubicin and included grade 4 neutropaenia (without neutropaenic fever) in all patients, renal toxicity and thrombocytopenia. Complete responses were observed in 89% of evaluable patients.[14]

Based on these data, we designed a prospective randomised trial to compare Carboplatin and Paclitaxel (standard arm) with Cisplatin, Paclitaxel and Doxorubicin plus G-CSF support (investigational arm) in the treatment of advanced epithelial ovarian cancer.

2. Objectives

The main objective was to evaluate overall survival (OS) and progression-free survival (PFS) and to compare possible differences between the two treatment arms. Secondary endpoints were to compare response rate and toxicity profile, which was expected to be of major importance for the Cisplatin, Paclitaxel and Doxorubicin arm.

3. Patients and methods

This was a prospective, multicentre, phase III study. Patients were enroled in 14 Oncology Centres in Greece.

To be eligible for the study, patients had to meet all the following inclusion criteria: (i) Histologically confirmed epithelial ovarian carcinoma FIGO stage IIc, III or IV. (ii) No previous chemotherapy, (iii) Laboratory values within normal levels (iv) Performance status (ECOG) $\leqslant$ 2, (v) No symptoms or signs of cardiac failure or acute coronary disease, (vi) Enrolment within six weeks from laparotomy, (vii) Patients' informed consent was necessary. There was no age restriction.

Patients with non-measurable or evaluable disease with either elevated or normal CA-125 levels at baseline were eligible for the study, but they were not evaluable for clinical response to chemotherapy.

Exclusion criteria included: (i) Other malignancy, except from non-melanoma skin cancer or radically excised *in situ* carcinoma of the cervix. (ii) History of atrial or ventricular arrhythmias and/or history of congestive heart failure; history of clinically and electrocardiographically documented myocardial infarction within the last 6 months or abnormal left ventricular ejection fraction (LVEF). (iii) Active infection or other serious medical conditions which would impair the ability of the patient to receive the treatment. (iv) Administra-

tion of other therapeutic drugs or hormonal therapy during the study period. (v) Patients with complete bowel obstruction and/or with brain metastases.

4. Treatment plan

Patients were stratified according to stage (IIc *versus* III *versus* IV), and the presence of residual disease and were randomised to receive either Paclitaxel with Carboplatin (group A) or Paclitaxel with Carboplatin alternating with Cisplatin (group B) as follows:

Arm A: Paclitaxel	175 mg/m^2	cycles 1–6
Carboplatin	7 AUC	cycles 1–6
Arm B: Paclitaxel	175 mg/m^2	cycles 1–6
Doxorubicin	40 mg/m^2	cycles 1–6
Cisplatin	75 mg/m^2	cycles 1–6
G-CSF (Lenograstim)	0.263 mg sc from days 7 to 11	

Treatment was given every 3 weeks. All patients received six courses of chemotherapy unless evidence of progressive disease or unacceptable toxicity was reported. Doxorubicin was always administered before Paclitaxel. Doxorubicin was administered as an IV bolus infusion. Paclitaxel was always administered before the platinum derivative. Dexamethasone 20 mg i.m or i.v 12 h and 6 h prior to Paclitaxel infusion, Cimetidine (150 mg i.v) and dimethydene maleate 4 mg i.v or promethazine 50 mg i.m. 30 min prior to Paclitaxel infusion were administered as premedication. Standard antiemetic treatment included Ondansetron 16 mg i.v 15 min prior to Paclitaxel infusion and Ondansetron 8 mg every 12h per os on day 2. Paclitaxel was administered in dextrose 5% or Normal Saline (NS) as 3-h continuous infusion. Carboplatin was administered as a short infusion IV diluted in 250 ml N/S or Dextrose 5%. The AUC (Area under the plasma concentration *versus* time curve) was calculated according to the Calvert formula.[15] Creatinine clearance was calculated based on the creatinine level, the age and patient's BSA by the method proposed by Jelliffe.[16] Cisplatin was administered either on an inpatient or outpatient basis. Cisplatin was administered on an outpatient basis only if preceded by adequate pre hydration.

Complete blood count (CBC), liver and kidney function tests, electrolytes, chest X-ray, ECG, abdominal CT scan and CA-125 determination were performed prior to initiation of chemotherapy. CBC was measured on the 14th day of the first cycle and thereafter if indicated. CBC, liver and kidney function tests were repeated at each cycle.

Dose modifications due to haematological toxicity: Patients proceeded with chemotherapy only if ANC was $\geqslant 1.5 \times 10^9$/l and platelet count $\geqslant 100 \times 10^9$/l. A week's delay was allowed for ANC recovery otherwise patients had to be treated with Granulocyte Colony Stimulating Factor (G-CSF) (lenograstim 0.263 mg). A maximum of 2 weeks delay was allowed for platelet recovery otherwise patients went off protocol. If platelet recovery occurred within 1week, the next treatment was repeated every 4 weeks. If two weeks were required for platelet recovery, the next courses were repeated again every 4 weeks but with a 25% reduction of the doses of all drugs. For grades 3 and 4 thrombocytopaenia during treatment, a reduction of 25% and 50%, respectively, was applied. If the patient developed febrile neutropaenia, G-CSF was administered prophylactically in the following courses.

Dose modifications due to non-haematological toxicity: For each 20 ml/min reduction of the creatinine clearance, a 25% dose reduction of the dose of Cisplatin was applied. For WHO Grade > 2 mucositis, 25% dose reduction of all drugs was introduced. For WHO Grade > 2 neurotoxicity, treatment had to be stopped. Paclitaxel was stopped in case of severe hypersensitivity reactions or severe cardiac toxicity (symptomatic ventricular arrhythmias, more than 1st degree AV block).

5. Response evaluation

Assessment of tumour response was performed every three cycles, unless clear evidence of progression was observed. Patients with either disease progression before the third cycle or discontinuing treatment due to toxicity or personal reasons (consent withdrawal) were considered treatment failures.

6. Statistical analysis

For a two-sided test at the 5% level of significance and power of 85%, the number of patients required to detect a 50% increase in median survival time to a baseline median at the 3-year time point was 430. The study accrual rate was estimated at 90 patients per year. This accrual corresponds to a maximum study duration of 6.4 years for observing 223 events. Taking into consideration a 5% withdrawal rate, the total number of patients was increased to 452 (226 per group).

An interim analysis based on the O'Brien Fleming boundary values was scheduled when 50% of the main end-point (111 deaths) had been reached. The study was scheduled to be ended prematurely if a significant difference was detected at interim analysis.

World Health Organisation (WHO) criteria for toxicity and response were applied.[17] OS was defined as the time interval between randomisation and date of death from any cause. Patients still alive were censored on the date of last contact. PFS was calculated from randomisation to the date of progression of the disease which was firstly documented, or to the date of death as a result of any cause. Patients who were still alive without progressive disease at the time of analysis were censored at the date of last contact.

Fisher's exact test was used for comparing patients' characteristics, response and toxicity. Exact binomial 95% confidence intervals (CIs) were used to determine the 95% upper and lower confidence limits of response rate. Time to event data were analysed using the Kaplan-Meier method, and the log-rank test was used to compare time to event distributions between groups.

Cox proportional hazards regression models were used to assess the influence on OS and PFS of age, PS (0 *versus* 1–2), presence of residual disease (no *versus* yes), stage (IIc *versus* III *versus* IV) and treatment group (group A *versus* group B). The Wald χ^2 test and the corresponding p-values were used

to determine significance. All statistical tests were two-sided and performed at a significance level of 0.05.

All end-points except response, toxicity and treatment characteristics were analysed according to the intent-to-treat (ITT) principle (all eligible patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment). Treatment characteristics and safety analyses were based on the actual treatment administered, whilst response was evaluated amongst patients with measurable or evaluable disease at baseline.

7. Results

Between February 1999 and March 2004, 469 patients were enroled in the study. Eighteen (4%) were found ineligible. Reasons for ineligibility were other than ovarian cancer diagnosis (3 patients), wrong stage of disease (5), history of previous cancer (2), creatinine clearance < 50 ml/min (2), interval from surgery more than 6 weeks (4) and other reasons (2). Four patients randomised in group B never started treatment (Fig 1).

The treatment groups were well balanced (Table 1) for baseline patient and disease characteristics ($p > 0.05$), with PS as the only exception ($p = 0.046$). Median age was 60 and 59 years, respectively. 69% of the patients had stage III and 23% stage IV disease. The majority of patients had serous histology (69.5% *versus* 66%). Fifty nine percent (59%) of patients presented with residual disease $\geqslant 2$ cm after the initial operation. 66% of patients in group A and 58% in group B had performance status (PS) 0 in ECOG scale ($p = 0.02$).

8. Toxicity and compliance with treatment

The incidence of grade III or IV acute toxicities in the two groups of patients is shown in Table 2. Treatment was generally well tolerated and there were no differences between the two groups ($p > 0.05$), with the exception of febrile neutropaenia, which was higher in group B (4% *versus* 12%, $p = 0.006$).

There were five toxic deaths (1 *versus* 4) during the treatment period. Three occurred during febrile neutropaenia, one was caused by haemorrhage and one was caused by dyspnoea during neutropaenia. All but one of these patients had poor (PS = 2) performance status.

A total of 2369 cycles of chemotherapy (1255 *versus* 1114, 5.5 cycles per patient) were delivered. Almost 87% of the cycles were given at full dose (>90% of the dose defined in the protocol). It appears that we were able to deliver more than 90% of the planned dose intensity (DI) for Paclitaxel in both arms (relative DI 0.94 *versus* 0.93), whilst the DI for Cisplatin

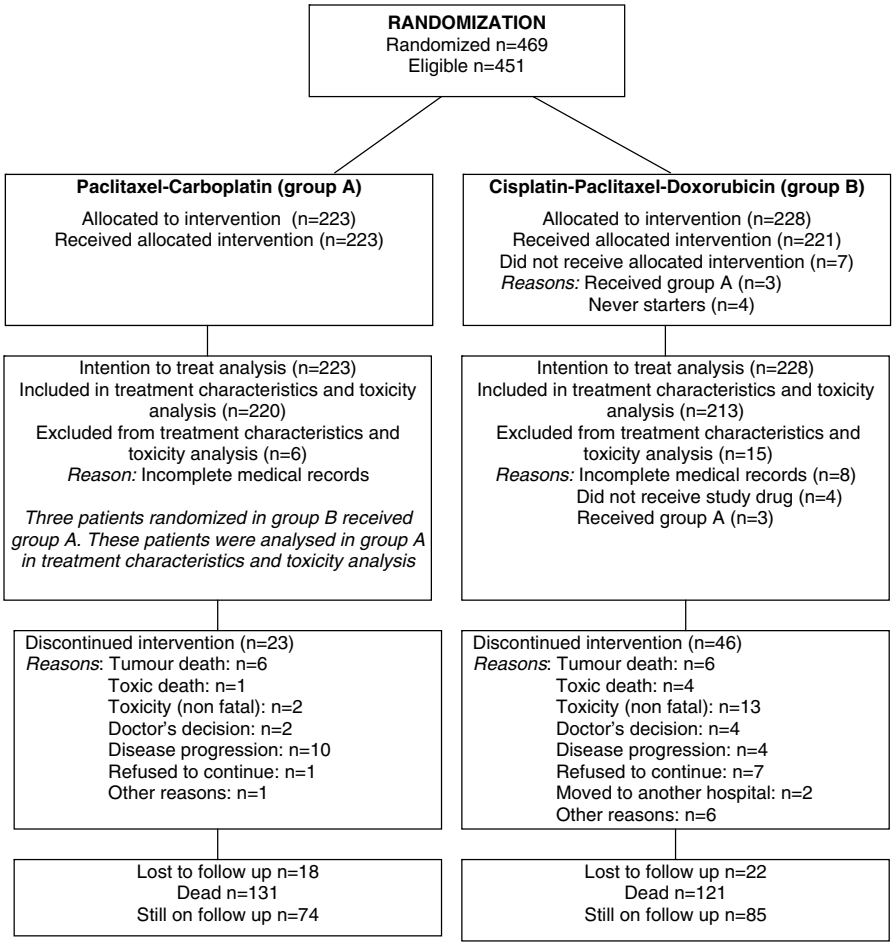

Fig. 1 – Progress through the various stages of the trial. Survival status updated on September 2006.

Table 1 – Selective patient and tumour characteristics

	Group A[a] (= 223)		Group B[b] (= 228)	
Age (years)				
Median	60		59	
Range	25–79		22–82.5	
	N	%	N	%
ECOG performance status[c]				
0	147	66	133	58
1	67	30	76	33
2	7	3	18	8
Unknown	2	1	1	0.4
Initial staging				
IIc	19	8.5	16	7
III	151	68	162	71
IV	53	24	50	22
Histology				
Serous	155	69.5	150	66
Mucinous	12	5	12	5
Endometrioid tumours	29	13	16	7
Clear cell tumours	3	1	6	3
Other histology[d]	24	10.5	44	19
Tumour grade				
I	15	7	15	7
II	60	27	65	28.5
III	114	51	100	44
IV	4	2	8	3.5
Undefined/Unknown	30	13.5	40	17.5
Residual disease				
< 2 cm	96	43	90	39.5
⩾2 cm	127	57	138	60.5

a Group A: Paclitaxel-Carboplatin.
b Group B: Paclitaxel-Cisplatin-Doxorubicin.
c $p = 0.046$, all other comparisons non-significant at 5% level.
d Mixed, undifferentiated carcinomas, unclassified epithelial tumours.

was 0.93. According to calculations based on the dose of Carboplatin at first cycle (expressed according to Body Surface Area with no corrections for changes of the creatinine clearance for the following cycles), it appears that roughly 90% of the initially planned dose of Carboplatin was actually delivered for group A.

9. Response, survival and progression-free survival

A total of 327 (72%) patients (163 *versus* 164) were assessable for response to chemotherapy. Overall Response Rate (ORR) was 69% (95% C.I: 61–76%) in group A and 64% (95% C.I: 56–71%) in group B ($p = 1.0$). Complete Response Rates (CRRs) were 43% and 36%, respectively.

With a median follow-up of 57.5 months, 315 patients (70%) demonstrated disease progression (164 *versus* 151). A marginal significance towards improved PFS was observed in group B [median PFS: 13.25 months (range: 0.01–90.98) *versus* 18.13 months (range: 14.78–21.48), log-rank $p = 0.07$] (Fig 2). Two hundred and fifty two patients (56%) died (131 *versus* 121). Median OS was 37.97 months (range, 0.01–90.98+) in group A and 44.33 months (range, 0.01–90.46) in group B (log-rank $p = 0.53$, Fig 2).

The estimated 5-year PFS rates were 22.2% (95% C.I: 16–28%) vs 26.6% (95% C.I: 20–33%), whilst the estimated 5-year OS rates being 38.9% (95% C.I 31–45%) *versus* 40.6% (95% C.I 33–48%) (Table 3).

At multivariate analysis, in the presence of randomisation group ($p = 0.23$), factors significantly associated with an increased risk of death were age [Hazard ratio (HR) = 1.01, 95% CI: 1.00–1.03, $p = 0.03$), PS (1–2 *versus* 0: HR = 2.19, 95% CI: 1.67–2.86, $p < 0.001$), stage (III *versus* IIc: HR = 2.67, 95% CI: 1.22–5.82, $p = 0.01$; IV *versus* IIc: HR = 3.71, 95% CI: 1.63–8.43, $p = 0.002$) and presence of residual disease (⩾2 cm *versus* <2 cm: HR = 1.33, 95% CI: 0.98–1.79, $p = 0.06$) (Table 4).

The hazard of disease progression at any time was significantly decreased by 25.5% for patients treated in group B compared to group A (group B *versus* group A: HR = 0.745, 95% CI: 0.60–0.93, $p = 0.009$). Additionally, PS (1–2 *versus* 0: HR = 1.87, 95% CI: 1.48–2.37, $p < 0.001$), stage (III *versus* IIc: HR = 2.20, 95% CI: 1.23–3.92, $p = 0.008$; IV *versus* IIc: HR = 3.0, 95% CI: 1.61–5.59, $p = 0.001$) and residual disease (⩾2 cm *versus* <2 cm: HR = 1.41, 95% CI: 1.09–1.82, $p = 0.01$) were related to significantly poorer PFS (Table 4).

In terms of time to treatment failure (TTF), defined as the interval from randomisation to the date of progression of disease, discontinuation of treatment or death due to any cause (whichever occurred first), no significant difference was found between the two groups both in univariate (median TTF, group A: 13.08 *versus* group B: 14.39, log-rank $p = 0.827$) and multivariate analysis (HR = 0.91, 95% C.I.: 0.73–1.13, $p = 0.40$).

10. Discussion

Despite the encouraging results from phase II studies, until recently, there was no evidence from a randomised trial that addition of a third drug either concurrently or sequentially could improve the long-term results obtained more than ten years ago with the incorporation of Paclitaxel in the first-line treatment of advanced ovarian cancer either with Cisplatin[1,3] or Carboplatin.[5–7] The combination of Carboplatin with Paclitaxel is considered a global standard for the treatment of Epithelial Ovarian Cancer and Primary Peritoneal Carcinoma. Although effective, most patients treated with this regimen recur and finally die of resistant disease. Therefore new combinations are needed.

In this study we examined the contribution of adding anthracycline, in particular doxorubicin to a Platinum/Paclitaxel combination. We chose Doxorubicin instead of Epirubicin since this is the anthracycline that has been more extensively studied as part of first-line chemotherapy in ovarian cancer.[10–14] Furthermore, we chose Cisplatin over Carboplatin to avoid the cumulative myelotoxicity of the Carboplatin/doxorubicin combination. Unfortunately, within the limitations of our sample size, our trial failed to demonstrate a benefit in adding anthracycline to the current standard Platinum/Paclitaxel regimen in terms of overall survival. In terms of PFS, the study showed a marginal

Table 2 – Incidence (%) of severe toxicities

N	Group A[a]				Group B[b]			
	220				213			
	Grade 3		*Grade 4*		*Grade 3*		*Grade 4*	
	N	%	N	%	N	%	N	%
Anaemia (A: 216, B: 207)	16	7.4	1	0.5	20	9.7	1	0.5
Leukopenia (A: 216, B: 207)	34	15.7	3	1.4	24	11.6	13	6.3
Neutropaenia (A: 216, B: 207)	54	25	38	17.6	31	15	39	18.8
Thrombocytopenia (A: 216, B: 207)	11	5.1	3	1.4	7	3.4	3	1.4
Nausea/Vomiting (A: 216, B: 206)	3	1.4	–	–	6	2.9	–	–
Diarrhoea (A: 216, B: 204)	3	1.4	–	–	3	1.5	1	0.5
Infection (A: 216, B: 204)	1	0.5	1	0.5	–	–	–	–
Fever (A: 220 B: 212)	–	–	–	–	2	0.9	–	–
Hepatotoxicity (A: 215, B: 206)	2	0.9	–	–	–	–	–	–
Neurotoxicity (A: 216, B: 204)	5	2.3	–	–	–	–	–	–
CNS[c] (A: 215, B: 205)	–	–	–	–	1	0.5	–	–
Cardiotoxicity (A: 215, B: 205)	–	–	–	–	1	0.5	–	–
Athralgias/Myalgias (A: 216, B: 203)	6	2.8	1	1	1	0.5	–	–
HSR[d] (A: 220, B: 213)	2	0.9	–	–	5	2.3	1	0.5

a Group A: Paclitaxel - Carboplatin.
b Group B: - Paclitaxel - Cisplatin - Doxorubicin.
c Central nerrous system.
d Hypersensitivity reactions.

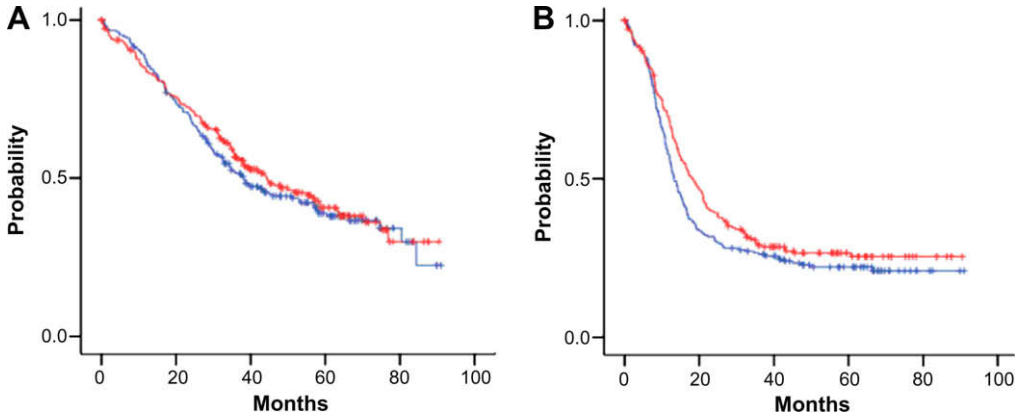

Fig. 2 – Overall survival (A) (p = 0.53) and PFS (B) (*p* = 0.07) of patients treated with Paclitaxel-Carboplatin or with Cisplatin–Paclitaxel–Doxorubicin.

improvement whilst in terms of TTF there is no difference between the two arms.

A very important relevant report by du Bois et al. came from AGO and GINECO in Europe.[18] They compared Carboplatin-Paclitaxel (TC) with Epirubicin added to the same combination (TEC). Median progression-free survival time was 18.4 months for the TEC arm and 17.9 months for the TC arm ($p = 0.3342$), whilst median overall survival time was 45.8 months for the TEC arm and 41.0 months for the TC arm ($p = 0.3652$). The authors concluded that the trial showed lack of benefit in adding an anthracycline to a modern platinum-based, Paclitaxel containing regimen. Similar results to the AGO/GINECO study have been preliminarily reported by a GICG trial comparing again TC *versus* TEC with a somewhat higher Epirubicin dose.[19,20]

Comparing the results of the AGO/GINECO with those from our study, a similar difference of almost 5 months and 7 months, respectively, in favour of the anthracycline arm is noted which, however, does not reach statistical significance. Possibly, in our study, the small difference in terms of PS in the anthracycline arm could have influenced this outcome. There was a non-significant almost 10% reduction in HR for death in the AGO/GINECO study compared with almost 15% reduction in our study. Obviously this benefit is traded off by higher toxicity in the anthracycline-containing arms.[18] In terms of PFS, we found a marginally significant difference ($p = 0.07$) in favour of the anthracycline arm. Again comparing our trial with the AGO/GINECO study it appears that this difference comes mainly from the lower PFS in the control arm (13.25 *versus* 18.3 months in our study, 17.9 *versus* 18.4 months

Table 3 – Overall Survival (OS), Progression-Free Survival (PFS)

	Group A (= 223)	Group B (= 228)	Log rank *p*-value
OS			
Events	131/223	121/228	
Range (months)	0.01–90.98+	0.01–90.46	
Median	37.97	44.33	0.53
95% C.I	29.83–46.10	33.13–55.53	
1-year OS rate (95% C.I)	87.4% (83–92%)	84% (79.5–89%)	
3-year OS rate (95% C.I)	51.5% (45–58%)	56.6% (50–63%)	
5-year OS rate (95% C.I)	38.9% (31–45%)	40.6% (33–48%)	
PFS			
Events	169/223	158/228	
Range (months)	0.01–90.98	0.01–90.46	
Median	13.25	18.13	0.07
95% C.I	11.50–14.99	14.78–21.48	
1-year PFS rate (95% C.I)	57.1% (50–64%)	68% (62–74%)	
3-year PFS rate (95% C.I)	26.2% (20–32%)	29.1% (23–35%)	
5-year PFS rate (95% C.I)	22.2% (16–28%)	26.6% (20–33%)	

Group A: Paclitaxel + Carboplatin; Group B: Cisplatin + Paclitaxel + Doxorubicin.

Table 4 – Estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS-Multivariate analysis

	HR	95% CI	p-value
Overall survival			
Treatment group			
Group A	1		
Group B	0.86	0.67–1.10	0.23
Age	1.01	1.00–1.03	0.03
PS			
0	1		
1–2	2.19	1.67–2.86	<0.001
Initial staging			
IIc	1		
III	2.67	1.22–5.82	0.01
IV	3.71	1.63–8.43	0.002
Residual disease			
<2 cm	1		
⩾2 cm	1.33	0.98–1.79	0.06
Progression-free survival			
Treatment group			
Group A	1		
Group B	0.745	0.60–0.93	0.009
PS			
0	1		
1–2	1.87	1.48–2.37	<0.001
Initial staging			
IIc	1		
III	2.20	1.23–3.92	0.008
IV	3.0	1.61–5.59	0.001
Residual disease			
<2 cm	1		
⩾2 cm	1.41	1.09–1.82	0.01

Group A: Paclitaxel-Carboplatin; Group B: Paclitaxel-Cisplatin-Doxorubicin.

in the du Bois study). What seems quite important in our results is that at multivariate analysis where the difference between the two arms in terms of PS has been taken into consideration, there is a statistically significant, almost 25%, reduction of the HR for disease progression in favour of the investigational arm. Unfortunately, this difference does not translate into a benefit in terms of survival.

The long awaited Intergroup study GOG0182-ICON5 was reported at 2006 ASCO meeting.[21] This was a large (more than 4000 patients) randomised 5-arm comparison in first-line chemotherapy in advanced ovarian cancer. The control arm was Carboplatin/Paclitaxel. There were two triplet combinations one with Gemcitabine, and the other with Liposomal Doxorubicin, and two sequential regimens in which after 4 cycles of Carboplatin/Gemcitabine or Carboplatin/Topotecan doublets, another 4 cycles of Carboplatin/Paclitaxel were given. The authors concluded that there was no evidence that adding a third active cytotoxic agent prolongs PFS or OS for the regimens evaluated.

Regarding the GOG0182 study, one could argue that in the anthracycline arm the planned dose intensity for Liposomal Doxorubicin was rather low (5 mg/m^2 per week). Perhaps this comparison could be used in a different design either as a triplet with higher dose of Liposomal Doxorubicin or as a sequential regimen, for example, 4 cycles of standard Carboplatin/Paclitaxel followed by 4 cycles of Carboplatin/Liposomal Doxorubicin. It is expected that in the near future, comparative efficacy results for Carboplatin/Paclitaxel *versus* Carboplatin/Liposomal Doxorubicin in first-line chemotherapy will be available.[22]

The optimism about the incorporation of other cytotoxic drugs to the standard Carboplatin/Paclitaxel disappeared after the negative results of several randomised trials. However, the results of a recent randomised phase II trial from Italy testing the feasibility and efficacy of Epirubicin and Ifosfamide added to chemotherapy with Cisplatin and Paclitaxel[23] renewed the interest. After a median follow-up of 82 months, median overall survival (OS) was 51 and 65 months, respectively; 5-year survival rates were 43% and 50%, respectively. Taking into consideration that more than 50% of patients in this report were suboptimally debulked after the first surgery, the authors concluded that OS seemed

to be longer than commonly reported. According to the authors this rather unexpected finding might have been partly a consequence of the aggressive chemotherapeutic approach.

Perhaps the issue of the role of a third cytotoxic drug is not completely closed. Many parameters should be taken into account, one of which is the higher toxicity of the triplets. Another important point is the possible need of utilising Cisplatin instead of Carboplatin as the platinum compound of choice in such regimens. It is difficult to confirm a marginal survival benefit from adding anthracycline to the standard Platinum/Paclitaxel regimen, with the limitations of the studies described above. Despite all efforts thus far, the outcome of the Platinum/Paclitaxel combination remains too hard to beat. Optimistic expectations have been raised recently with the preliminary encouraging results reported when targeted agents such as Bevacizumab,[24] Cetuximab,[25] Erlotinib[26] and others [27] were added to the standard first-line chemotherapy.

Conflict of interest statement

None declared.

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