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Paclitaxel/carboplatin versus topotecan/paclitaxel/carboplatin in patients with FIGO suboptimally resected stage III–IV epithelial ovarian cancer a multicenter, randomized study

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ABSTRACT

Objective: The objective of this prospective randomized phase III trial was to compare paclitaxel plus carboplatin (PC) versus topotecan plus carboplatin and paclitaxel (TPC) in women with suboptimal stage III (residual tumour >1 cm) or stage IV ovarian cancer to evaluate the survival rate and toxicities.

Methods: Eligible for the study were patients aged at least 18 years old with histological/cytological diagnosis of FIGO stages III (residual tumour ⩾1 cm after primary surgery) – IV epithelial ovarian cancer. Patients were randomized to iv PC on day 1, every 21 days or iv topotecan daily for three days and PC on day 3, every 21 days.

Results: The intention to treat population was made of 326 patients in total, 170 in the PC group and 156 in the TPC group. The life table estimates of survival probabilities at one, three and five years were, respectively, 0.94 (95% CI: 0.88–0.97), 0.53 (95% CI: 0.44–0.62) and 0.32 (95%CI: 0.23–0.42) in the PC group, and 0.92 (95% CI: 0.86–0.95), 0.52 (95% CI: 0.42–0.61), and 0.32(95%CI: 0.22–0.43) in the TPC group (log-rank test at 5 years: ns). The results of the survival analysis based on Cox regression model showed no statistically significant differences between groups (*p*-value: ns). The number of subjects with at least one event with possible relationship to study medication was 151 (88.8%) in the PC group and 139 (89.1%) in the TPC group (*p* = ns).

Results: In the PC group, 79 patients (23.6%) experienced at least one Adverse Event (AE) graded as severe and 16 patients (4.8%) at least one life-threatening AE, whilst in the TPC

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group, the number of patients who presented at least one severe or life-threatening AE was 86 (24%) and 37 (10.3%), respectively.

Conclusion: The results of the present study show that the addition of topotecan to a standard paclitaxel/carboplatin regimen in the treatment of advanced epithelial ovarian cancer did not result in significant advantages in terms of survival rate. A slightly worse toxicity profile for TPC was observed.

1. Introduction

The therapy for advanced ovarian carcinoma is maximal surgical cytoreduction followed by chemotherapy.

Several trials showed that paclitaxel–carboplatin (PC) combination is as effective as paclitaxel and cisplatin[1–3] with a better safety profile.

Regimens including a carboplatin plus paclitaxel have become the preferred first-line therapy.

Despite the progress that has been achieved over the years, survival rates in patients with advanced ovarian cancer are still disappointing.[4]

Thus topotecan, gemcitabine, and anthracyclines have been included into first-line regimens for advanced ovarian cancer.[5–10]

According to previous experience of a salvage treatment including carboplatin on day 3 and topotecan as a 3-day administration,[5] on 2000 started a prospective randomized phase III trial to compare PC versus topotecan plus carboplatin and paclitaxel (TPC) in women with suboptimal stage III (residual tumour >1 cm) or stage IV ovarian cancer to evaluate the survival rate and toxicities.[11] In this paper we report the final results.

2. Methods

This is an open-label, multicentre, randomized study designed to evaluate the efficacy and the toxicities of the association PC versus TPC in patients with FIGO stage III (residual tumour >1 cm) – IV epithelial ovarian cancer.

Eligible for the study were patients aged at least 18 years old with histological/cytological diagnosis of FIGO stages III (residual tumour $\geqslant$1 cm after primary surgery)–IV epithelial ovarian cancer; performance Status $\leqslant$2 (ECOG scale); a life expectancy of at least 3 months; presence of at least one indicator lesion to be used for assessment of response (preferably surgery (laparoscopy or laparotomy); no prior chemotherapy; laboratory values: WBC $\geqslant 3.5 \times 10^3$ μl, haemoglobin $\geqslant$ 9.0 g/dl, neutrophils $\geqslant 1.5 \times 10^3$ μl, platelets $\geqslant 100 \times 10^3$ μl, creatinine $\leqslant$ 1.5 mg/dl, or creatinine clearance $\geqslant$ 60 ml/min, serum bilirubin $\leqslant$ 2.0 mg/dl, SGOT, SGPT, and alkaline phosphatase $\leqslant$ 2 times the upper limit of normal; no noteworthy ECG abnormalities.

Exclusion criteria were concomitant malignancies or previous malignancies within the last five years (excepting basal or squamous cell carcinoma of the skin and carcinoma *in situ* of the cervix); CNS and/or leptomeningeal metastases; concurrent severe medical problems unrelated to the malignancy which would significantly limit full compliance with the study; history of cardiac diseases, other concurrent chemotherapy, immunotherapy, radiotherapy, or any other investigational medication for the treatment of the tumour; prior treatment with other chemotherapy regimen.

Eligible patients were randomized by phone by the coordinating centre to receive either iv PC on day 1, every 21 days or iv daily topotecan for three days and PC on day 3, every 21 days.

Study participants were stratified according to FIGO stage of disease (stage III versus stage IV versus carcinosis) and participating centre.

The randomization started in February 2000 and ended in December 2003.

2.1. Group PC

Paclitaxel 175 mg/m^2 was administered as a 3-h infusion followed by carboplatin AUC 5 given as a 30-min infusion on day 1 every 21 days for 6 cycles. Carboplatin dosage was calculated according to the Cockroft and Gault formula.

2.2. Group TPC

Topotecan 1.0 mg/m^2 was administered intravenously over 30 min for three days (day 1–3). Paclitaxel at a dose of 175 mg/m^2 given as a 3-h infusion followed by carboplatin AUC 5 given as a 30-min infusion were administered on day 3 every 21 days for 6 cycles. On day 3, the patients got the 3 drugs.

Topotecan dose was not reduced (unless the toxicity was believed to be related to topotecan. In this case, the protocol foresaw to reduce the dose to 0.8 mg/m^2). Carboplatin and paclitaxel were cut to AUC 4 and 150 mg/m^2, respectively, if the platelet count was $<75 \times 10^3$ μl or the granulocyte count was $<1.0 \times 10^3$ μl for >7 days at nadir, despite G-CSF therapy in the latter case.

Chemotherapy administration started within 5 weeks since surgery.

During the 6 cycles' period, patients with progressive disease (PD) suspended the study treatment as soon as the progression was detected.

Standard premedication included: clorfenamine maleatum 10 mg im 1 h before starting paclitaxel, cymetidin 300 mg iv, and hydrocortisone sodium succinate 500 mg iv 30 min before starting paclitaxel.

Centres were free to perform interval debulking surgery in responding patients in which primary surgery was explorative, laparoscopy, or laparotomy.

Second look surgery was allowed in responding patients with negative CA 125 after 6 cycles of chemotherapy. During second look surgery it was possible to remove residual tumour in patients with partial response (PR).

Indicators for response evaluation were second look surgery or indicator lesion. These lesions had to meet the criteria for measurable or valuable disease and had to be defined by a tumour imaging assessment (including CT or MRI scan, ultrasound, or chest X-ray), or physical examination. The same diagnostic imaging method was used throughout the study to evaluate the lesions.

Additional chemotherapy, including maintenance or consolidation was not allowed till the progression of the disease.

For patients who did not progress on study and completed the treatment, the investigator conducted the post-treatment assessments every 3 months during the first year, every 4 months during the second year, and every 6 months during the third and the fourth year.

The study protocol did not provide any indication for second line treatment of patients. However, the general policy of participating centres included second-line chemotherapy with a platinum-based compound in case of late recurrence or progression of the disease (i.e. >12 months after first-line treatment) and a treatment including anthracyclines in case of early recurrence/progression.

Follow up was updated on 2007.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki and received the approval by the Review Boards of the participating centres.

Patients had given their written informed consensus to the study.

2.3. *Statistical consideration and data analysis*

The computation of the sample size considered the main endpoint: survival. The purpose of this study was to compare the rate of overall survival at 3 years in patients receiving the combination of PC versus TPC.

The targeted sample size for this protocol was 350 patients.

Considering an overall survival rate in the PC group of 20% at 3 years from first diagnosis, this sample size was foreseen to be able to identify an increase in survival rate in the TPC group to 35% with 80% of power and alfa 0.05.

In consideration of the higher survival rate observed at 3 years in the PC group (about 40%), we have computed a post hoc computation of the power of the study: we are able to identify a difference in survival rate to 55% in the TPC group with 80% of power and alfa 0.05.

2.4. *Data analysis*

In consideration of the availability of follow up data at the moment of the preparation of the report of the study, 5-years survival rates are presented in this paper for the total population and 4-years survival rates for the analysis in strata of selected variables.

The primary efficacy variable was overall survival.

The secondary efficacy variables were progression free survival and response rate.

The progression free survival was defined as the time interval between randomization to the first documented sign of progression.

Complete response (CR) was defined as (per WHO criteria) complete disappearance of all known measurable and evaluable diseases for a period of at least four weeks. Partial response (PR) was defined as 50% or greater decrease in the sum of the products of the greatest length and perpendicular width of the largest measurement of all measurable lesions for at least four weeks with no simultaneous increase in a known lesion (>25%) or appearance of new lesions or increase in valuable disease during this period. Progression was defined as greater than 25% increase in the sum of the products of the measurable disease, reappearance of measurable disease, clear worsening of valuable disease, appearance of any new lesions, or significant worsening of conditions presumed to be related to malignancy.

Toxicity was recorded according to the WHO recommendations.

For efficacy analysis we considered all randomized patients who received at least one dose of study medication (intention to treat population, ITT).

The per protocol population (PP) included all the evaluable subjects according to the complete criteria defined in the study protocol.

For safety analysis we considered the ITT population.

Kaplan-Meier survival estimates were plotted and the survival probabilities in the two treatment groups were compared using the log-rank test. An additional survival analysis based on Cox regression was planned. The model included terms for performance status: 0–1 versus 2; FIGO staging: III versus IV; histotype: serous versus non-serous; FIGO grading: 1 versus 2/3; residual tumour: <2 cm versus 2–5 cm versus >5 cm and/or peritoneal carcinosis; age: $\leqslant$50 years versus >50 years and centre as covariates.

The percentages of patients who showed CR, PR, SD, and PD were summarised by treatment. The response rates in the two treatment groups were compared by means of the chi-square test or, where appropriate, by the Fisher's exact test.

The number of patients experiencing adverse events and the total number of adverse events (AE) that occurred during the study were calculated. Differences in the number of patients with at least one AE between the two treatment groups were tested using the chi-square test.

A summary of observed AE has been tabulated according to common toxicity grade (NCI CTC).

The following laboratory data were analyzed by summarising the CTC grade distribution for each visit and the worst CTC grade reported during the study: neutrophils, platelets, haemoglobin, and leucocytes.

The number of patients who underwent supportive therapy (transfusions or G-CSF) was presented for each treatment group.

3. Results

A total of 330 patients were enrolled in the study in 28 centres in Italy.

Four patients did not present any evidence of assumption of the study drugs. These patients were excluded from the ITT

population, represented by 326 patients in total, 170 in the PC group, and 156 in the TPC group.

The PP population included 257 patients in total, 133 in the PC group, and 124 in the TPC group (Fig. 1).

The distribution of study subjects according to selected characteristics and study group is shown in Table 1.

The study groups were similar with regard to age, histotype, stage, grade, residual tumour, and lymph nodal status distribution.

Since the first diagnosis, 166 patients (97.6%) in the PC group and 148 patients (94.9%) in the TPC group underwent surgical procedures for ovarian cancer.

In both treatment groups the most common surgical procedure was laparotomy, reported by 144 patients (86.7% of the subjects who had a surgical procedure) in the PC group and by 134 (90.5%) in the TPC group.

3.1. *Overall survival and progression free survival*

The results of the survival analysis are shown in Fig. 1. The life table estimates of survival probabilities at one, two and three, four and five years were, respectively, 0.94 (95% CI: 0.88–0.97), 0.71 (95% CI: 0.63–0.78), 0.53 (95% CI: 0.44–0.62), 0.41 (95% CI: 0.32–0.50), and 0.32 (95% CI: 0.23–0.42) in the PC group, and 0.92 (95% CI: 0.86–0.95), 0.77 (95% CI: 0.69–0.84), 0.52 (95% CI: 0.42–0.61), 0.41 (95% CI: 0.31–0.51), and 0.32 (95% CI: 0.22–0.43) respectively, in the PCT group.

The comparison between the two treatment groups was not statistically significant (log-rank test at 5 years: ns).

Analyses in strata of residual tumour, histotype, and grading showed no statistical difference on survival between both groups, however patients with residual tumour of 1–2 cm treated with the triple schedule tended to show a higher 4-year survival rate (0.48 versus 0.66) and subjects with carcinosis a lower one (0.53 versus 0.47 p ns) (Table 2).

The results of the survival analysis based on Cox regression model showed no statistically significant differences between groups (p-value: ns): the relative risk for TPC compared to PC was 0.85 (95% CI: 0.56–1.29).

The results in the PP population were consistent with those observed in the ITT analysis: the comparison between the two groups was not statistically significant (log-rank test: ns) (data not shown).

The results of the progression free survival analysis are summarised in Figs. 2a and 2b. The comparison between the two treatment groups was not statistically significant (log-rank test p-value: ns). This result was confirmed for the PP population (log-rank test p-value: ns, data not shown).

Data on objective response was available in for 137 patients in the PC and 126 in the TPC group. The results of response rates are shown in Table 3.

No significant differences were observed between the two treatment groups in the rate of complete or partial response between the groups (p-value: 0.62 for CR and 0.67 for PR). The results in the PP population were consistent with those observed in the ITT analysis (data not shown).

3.2. *Safety*

The number of subjects with at least one event with possible relationship to study medication was 151 (88.8%) in the PC group and 139 (89.1%) in the TPC group (p = ns).

In the PC group, 79 patients (23.6%) experienced at least one AE of severity graded as severe and 16 patients (4.8%) at

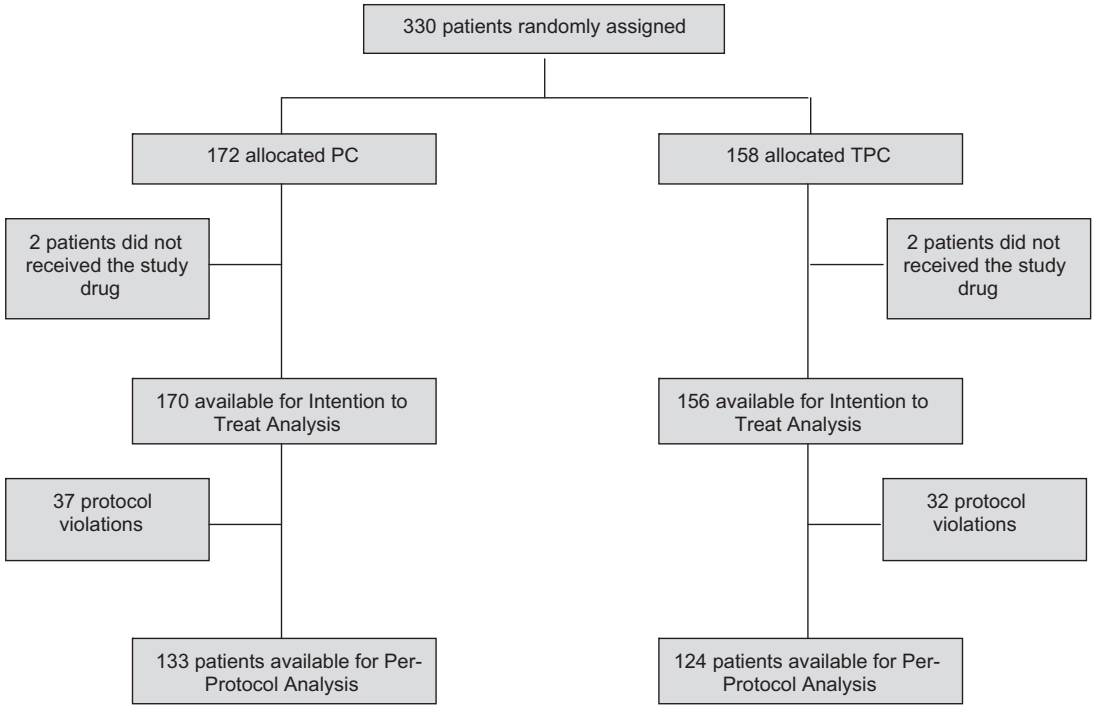


Fig. 1 – CONSORT trial flow diagram for patients accrued into the trial.

Table 1 – Characteristics of study patients.

	PC group (No. = 170)	TPC group (No. = 156)
Age in years		
(mean, DS, range)	57.4 ± 10.2 (31–78)	58.7 ± 9.4 (38–75)
Histotype		
Malignant serous tumours	116 (68.2%)	117 (75.0%)
Malignant mucinous tumours	4 (2.4%)	0 (0.0%)
Malignant endometroid tumours	16 (9.4%)	3 (1.9%)
Undifferentiated carcinoma	13 (7.6%)	19 (12.2%)
Malignant clear cells	11 (6.5%)	8 (5.1%)
Other	9 (5.3%)	9 (5.8%)
Not recorded	1 (0.6%)	0 (0.0%)
Grading (FIGO)		
1	2 (1.2%)	0 (0.0%)
2	30 (17.6%)	28 (17.9%)
3	115 (67.6%)	108 (69.2%)
Not recorded	23 (13.5%)	20 (12.8%)
Stage (FIGO)		
III	129 (75.9%)	123 (78.8%)
IV	41 (24.1%)	32 (20.5%)
Not recorded	0 (0.0%)	1 (0.6%)
Surgical procedures		
No	4 (2.4%)	8 (5.1%)
Yes	166 (97.6%)	148 (94.9%)
Residual tumour (cm)		
$\geqslant$1 and $\leqslant$2	20 (12.0%)	19 (12.8%)
>2 and $\leqslant$5	24 (14.5%)	22 (14.9%)
>5 and $\leqslant$10	14 (8.4%)	11 (7.4%)
>10	6 (3.6%)	5 (3.4%)
Peritoneal carcinosis	102 (61.4%)	91 (61.5%)
Site of residual tumour after primary surgery		
Abdominal/pelvic	165 (97.1%)	150 (96.2%)
Hepatic	22 (12.9%)	15 (9.6%)
Lymph node	15 (8.8%)	29 (18.6%)
Pulmonary	3 (1.8%)	6 (3.8%)
Other	8 (4.7%)	8 (5.1%)

Table 2 – Four year overall survival according to study group in the total population and in strata of selected characteristics.

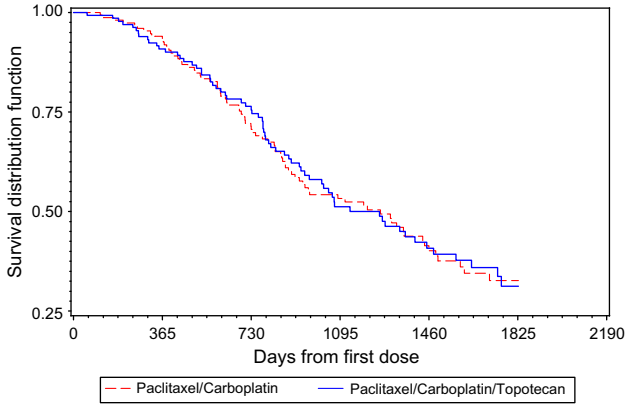
	PC group	TPC group	*P* value
	% Survival (95% confidence interval)	% Survival (95% confidence interval)	
Total population	41(32–50)	41(31–51)	n.s.
Residual tumour (cm)			
$\geqslant$1 to $\leqslant$2	48 (24–99)	66 (36–85)	n.s.
>2	57(40–70)	57(37–72)	n.s.
Carcinosis	53(41–64)	47(34–64)	n..s.
Histotype			
Serous tumour	50(39–60)	56(49–66)	n.s.
Other	61(44–74)	38(19–57)	n.s.
Grading			
1–2	53(31–71)	58(33–77)	n.s.
3	55(44–64)	52(40–63)	n.s.

n.s.: not significant.

least one life-threatening AE, whilst in the TPC group, the number of patients who presented at least one severe or life-threatening AE was 86 (24%) and 37 (10.3%), respectively.

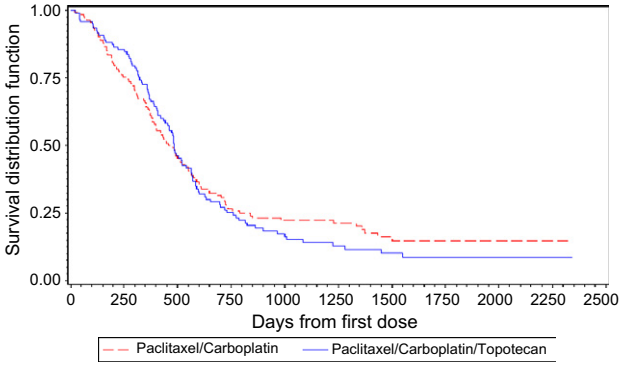
The most frequent AE are reported in Table 4.

Fatigue, anaemia, neuthopenia were significantly more frequent in the TPC group.



Time interval (days)	N. of pts with event	N. of pts censored
Paclitaxel/Carboplatin		
0 -365	10	27
365-730	31	11
730 -1095	21	12
1095-1460	12	14
1460 -1825	5	15
1825 2190	0	12

Fig. 2a – Kaplan-Meier survival plot: time to death.



Paclitaxel/Carboplatin/Topotecan		
0-365	12	28
365-730	17	15
730-1095	25	15
1095-1460	8	9
1460-1825	5	10
1825-2190	0	12

Treatment comparison: paclitaxel/carboplatin vs paclitaxel/carboplatin/topotecan Log-rank test Value 0.013, P-value 0.910

Fig. 2b – Kaplan-Meier survival plot on time to progression.

3.3. *Treatment modification*

The median duration of chemotherapy was 112 days (range 22–198) in the PC group and 115 days (range 24–192) in the TPC group (*p*: ns).

The number of patients with at least one course delay was 78 (49.1%) in the PC group and 76 (53.1%) in the TPC group (*p*: ns).

The number of patients with at least one paclitaxel dose reduction was 18 (11.3%) in the PC group and 40 (28.0%) in the TPC group (*p*: <0.001) and those with at least one carboplatin dose reduction was respectively 16 (10.1%) and 44 (30.8%) (*p*: <0.001).

Two patients (1.4%) at cycle 2 and 1 (0.8%) at cycle 3 required topotecan dose reduction.

The number of patients who completed six treatment cycles was 139 (82.2%) in the PC group and 121 (77.6%) in the TPC group (*p*: 0.29).

Table 3 – Response rate according to study group.

	PC group No. (%)	TPC group No. (%)	P value*
Complete response	67 (48.9%)	66 (52.0%)	
Partial response	43 (31.4%)	43 (33.9%)	
Stable disease	16 (11.7%)	6 (4.7%)	
Progressive disease	11 (8.0%)	11 (8.7%)	n.s.

n.s. not significant.
* Chi square heterogeneity.

3.4. *Supportive therapy*

The number of patients who received transfusions was 16 (11.6%) in the PC group and 32 (26.9%) in the TPC group (*p*: 0.002).

The number of patients who received G-CSF at the end of treatment was 10 (7.2%) in the PC group and 30 (25.2%) in the TPC group (*p*: <0.001).

4. Discussion

The primary objective of this study was to evaluate survival in the two following treatment regimens: PC versus TPC in patients with sub optimally-resected stage III or IV ovarian cancer.

The general results show that there were no statistically significant differences between the two treatment regimens in survival rate. Moreover, the comparison between both groups in terms of time to progression and response rate did not show any statistically significant difference.

With regard to safety and tolerability, the rate of drug-related adverse events was similar in the two groups, whilst the risk of drug-related serious adverse events was higher in the group of patients receiving additional topotecan.

The risk of anaemia and leucopenia was higher in the TPC than in the PC group and the percentage of patients requiring transfusions or supportive G-CSF therapy was lower in the PC group than in the TPC group.

The results of this study should be discussed in comparison with published data.

Several randomized clinical trials have tested the role of triple cytotoxic therapy for advanced ovarian cancer in comparison with standard treatment with carboplatin or cisplatin plus paclitaxel. Triple schedules included anthracycline, gemcitabine, and topotecan. In general no differences emerged.[12]

In particular, some studies randomized clinical trials and one phase II study have included topotecan in the triple schedule.

Table 4 – Summary of patients with adverse events by common toxicity grade.

	Paclitaxel/ carboplatin (N = 170)	Paclitaxel/ carboplatin/topotecan (n = 156)
Allergy		
Mild	8 (4.71%)	8 (5.13%)
Moderate	1 (0.59%)	4 (2.56%)
Severe	1 (0.59%)	5 (3.21%)
Life threatening	1 (0.59%)	0 (0.00%)
Not indicated	0 (0.00%)	1 (0.64%)
P value	ns	
Anorexia		
Mild	2 (1.18%)	1 (0.64%)
Moderate	1 (0.59%)	0 (0.00%)
P value	n.s.	
Arthralgia		
Mild	4 (2.35%)	5 (3.21%)
Moderate	4 (2.35%)	2 (1.28%)
P value	n.s.	
Fatigue		
Mild	2 (1.18%)	8 (5.13%)
Moderate	2 (1.18%)	0 (0.00%)
Severe	0 (0.00%)	1 (0.64%)
Not indicated	1 (0.59%)	0 (0.00%)
P value	0.05	
Febrile neutropenia		
Mild	0 (0.00%)	1 (0.64%)
Life threatening	0 (0.00%)	1 (0.64%)
P value	n.s.	
Nausea		
Mild	28 (16.47%)	31 (19.87%)
Moderate	16 (9.41%)	17 (10.90%)
Severe	1 (0.59%)	3 (1.92%)
P value	n.s.	
Neurotoxicity		
Mild	51 (30.00%)	47 (30.13%)
Moderate	6 (3.53%)	3 (1.92%)
Severe	2 (1.18%)	2 (1.28%)
Not indicated	0 (0.00%)	1 (0.64%)
P value	n.s.	
Mucositis		
Mild	0 (0.00%)	2 (1.28%)
Moderate	1 (0.59%)	1 (0.64%)
P value	n.s.	
Vomiting		
Mild	7 (4.12%)	9 (5.77%)
Moderate	8 (4.71%)	16 (10.26%)
Severe	1 (0.59%)	3 (1.92%)
Life threatening	0 (0.00%)	1 (0.64%)
P value	n.s.	
Thrombosis		
Severe	0 (0.00%)	1 (0.64%)
P value	n.s.	
Haemoglobin		
0 (>10 g/dL)	102 (60.0%)	50 (32.1%)
1 (=10 g/dL)	1 (0.6%)	3 (1.9%)
2 ($\geqslant$8 *e* < 10 g/dL)	64 (37.6%)	93 (59.6%)
3 ($\geqslant$6.5 < 8 g/dL)	2 (1.2%)	10 (6.4%)
4 (<6.5 g/dL)	1 (0.6%)	0 (0.0%)
P value	<0.01	
Leucocytes		
0 ($\geqslant 3.5 \times 10^3$ ul)	71 (41.8%)	51 (32.7%)
1 ($\geqslant 3$ e < 3.5×10^3 ul)	39 (22.9%)	27 (17.3%)
2 ($\geqslant 2$ e < 3×10^3 ul)	56 (32.9%)	61 (39.1%)
3 ($\geqslant 1$ e < 2×10^3 ul)	4 (2.4%)	17 (10.9%)
P value	0.004	
Neutrophils		
0 ($\geqslant 2 \times 10^3$ ul)	24 (14.1%)	29 (18.6%)
1 ($\geqslant 1.5$ e < 2×10^3 ul)	35 (20.6%)	23 (14.7%)
2 ($\geqslant 1$ e < 1.5×10^3 ul)	71 (41.8%)	42 (26.9%)
3 ($\geqslant 0.5$ e < 1×10^3 ul)	31 (18.2%)	52 (33.3%)
4 (<0.5×10^3 ul)	9 (5.3%)	10 (6.4%)
P value	0.004	

Note: only the event with the maximum toxicity grade was considered for each patient and AE.

In the analysis of the Gynaecologic Cancer InterGroup study, the patients who received PC plus topotecan reported a 3-weeks decrement in median progression free survival in comparison with patients receiving standard CP treatment.[10]

Pfisterer et al.[9] (2006) conducted a randomized trial including 1308 patients with stage IIB–IV ovarian cancer. These patients were randomized to receive six cycles of paclitaxel and carboplatin followed by either four cycles of topotecan or surveillance on a 3-week per cycle schedule. The median survival was 43.1 months for the topotecan group and 44.5 months for the surveillance one.

Further, in a small phase II study 343 patients with advanced ovarian cancer and >1 cm residual disease were treated with sequential carpoblatin (AUC 5 days 1 and 22) paclitaxel (1.75 mg m(–2) days 43 and 64) and topotecan 1.5 mg m(–2) daily for 5 days. The best overall response was 77% and the median survival was 22.2 months.[13]

The standard dose of topotecan as monotherapy in first or second line therapy for ovarian cancer is 1.5 mg/m^2 over 5 days. In the Gynaecologic Cancer InterGroup study, topotecan was given at in the dose of 1.25 mg/m^2. In the present series topotecan was given at the dose of 1.0 mg/m^2 over 3 days and the effective given dose was lower.

Delivery of the third drug in an adequate dosage is difficult.[12] Further, concomitant delivery of topotecan, paclitaxel with a platinum compound has been shown feasible with cisplatin,[14] but not with carboplatin.

Earlier phase I studies including topotecan and cisplatin suggested that myelosuppression was lower if cisplatin was given on day 5 rather than day 1.[12]

In this study carboplatin was given on day 3.

It has been suggested that more aggressive therapy may have greater impact in patients with small volume residual disease. Along this line, in the Gynaecologic Cancer InterGroup analysis, the TPC schedule showed a, not statistically significant, better survival rate than PC one in patients with microscopic residual tumour, but not with residual tumour $\leqslant$1 cm or >1 cm.[10]

We have analyzed overall survival rates in the strata of residual tumour, histotype and grading. No statistical difference emerged, but patients with residual tumour of 1–2 cm treated with the triple schedules had a higher, not significant, 4-year survival rate (0.66 versus 0.48).

In this analysis also progression free survival rates were similar in the two groups. In this study second look surgery was allowed. It has been shown that second surgical assessment of small-volume disease may change the determination of time to progression,[15] but in this randomized trial second look surgery was performed in both the groups in a similar frequency.

In conclusion, the results of the present study show that the addition of topotecan to a standard paclitaxel/carboplatin regimen in the treatment of advanced epithelial ovarian cancer did not result in significant advantages in terms of survival rate, time to progression and response. These findings are in general agreement with the result of the large data set of the Gynaecologic Cancer InterGroup study. A slightly worse toxicity profile for TPC as well as a more frequent need for more G-CSF was observed.

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Conflict of interest statement

None declared.

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