A Phase III Randomized Study Comparing Paclitaxel and Cisplatin *versus* Cyclophosphamide and Cisplatin in Patients with Advanced Ovarian Cancer

D. MOURATIDOU[1], C. GENNATAS[2], V. MICHALAKI[2], A. PAPADIMITRIOU[3], CH. ANDREADIS[1], C. SYKIOTIS[2] and N. TSAVARIS[4]

[1]Theagenion Hospital, Thessaloniki; [2]Areteion Hospital, University of Athens; [3]Nikaia General Hospital, Athens; [4]Laiko Hospital, University of Athens, Greece

Abstract. *Aim: To assess progression-free survival (PFS) and overall survival (OS) in patients with advanced epithelial ovarian cancer receiving the combination of cisplatin (75 mg/m^2 i.v.) and cyclophosphamide (700 mg/m^2 i.v.) (CP), or the combination of paclitaxel (175 mg/m^2) followed by cisplatin (75 mg/m^2) (TP). Patients and Methods: One hundred and twenty patients were randomized to receive six cycles of one of the treatments every 3 weeks. If measurable, complete response (CR) or partial response (PR) was determined. Results: There was a significant difference ($p<0.05$) in the frequency of response (CR+PR) rates between treatment groups, in favor of paclitaxel containing regimen. The median PFS was 9 months for patients in the CP group and 12 months for patients in the TP group (log-rank $p=0.215$). The median OS were 24 months and 20 months in TP and CP arms, respectively (log-rank $p=0.350$). Neutropenia and alopecia were more severe with paclitaxel-containing regimen. Conclusion: Although OS and PFS were similar in two arms, TP regimen yielded superior response rates relative to CP, with an acceptable toxicity profile. Therefore, the TP regimen remains the preferred initial treatment option.*

Surgery plays a crucial role in all phases of the management of ovarian cancer, however, is not curative due to dissemination of tumor cells throughout the abdominal cavity. Therefore, successful management generally requires additional treatment (1). The use of postoperative chemotherapy is standard for all patients with advanced-stage disease and for many patients with early-stage disease (2, 3). Cisplatin or cisplatin-based regimens have been the standard of care in women diagnosed with advanced epithelial ovarian cancer (4).

Despite the established benefits of platinum-containing regimens, the prognosis for long term survival of women who are suboptimally debulked remains unsatisfactory. With paclitaxel's activity established as a salvage treatment in phase II trials of patients with ovarian cancer (5), two consecutive randomized phase III trials were carried out assessing the potential value of paclitaxel in the first-line treatment of these patients (6). The results of these trials support a survival advantage for patients treated with combinations of *i.v.* platinum and paclitaxel, as compared with those given a platinum plus cyclophosphamide. As reported by McGuire *et al.*, the incorporation of paclitaxel into first-line therapy improves the duration of progression-free survival and of overall survival in women with incompletely resected stage III and stage IV ovarian cancer (7). Similarly, an analysis of the intergroup trial showed an improvement in median survival from 25 to 35 months in favor of the paclitaxel arm (8).

The aim of this study was to compare the activity, in terms of progression-free and overall survival, of the combination of paclitaxel and cisplatin *versus* cyclophosphamide and cisplatin in patients with advanced ovarian cancer.

Patients and Methods

Eligibility criteria. Eligible patients had histologically confirmed epithelial ovarian cancer, with International Federation of Gynecology and Obstetrics stage IIB-IV disease after initial debulking surgery. They could have clinically measurable or able to be evaluated disease. Registration to the study had to occur within 6 weeks after the surgical procedure. No prior anticancer treatment with drugs or radiation was allowed. Patients with a history of prior malignancy other than non-melanoma skin cancer were ineligible. Other eligibility requirements included normal marrow (granocytes>1500/μL; platelets>100,000 μL), renal (serum creatinine <2.0 mg/dl), and liver function (ALT, AST < two times normal; serum bilirubin<1.5 mg/dl); and WHO performance score of 0, 1, 2 or 3.

Correspondence to: Constantine Gennatas, MD, Areteion Hospital, University of Athens, 5, Arnis Street, 11528 Athens, Greece. Tel: +30210 7244758, e-mail: gennatas@otenet.gr

Key Words: Cyclophosphamide, paclitaxel, ovarian cancer.

Written informed consent fulfilling all institutional regulations was obtained from all patients before entry onto study.

Before study registration, patients underwent a baseline assessment, which included a review of their history, a physical examination, blood counts, chemistries, CA125 levels, and a postoperative computed tomography scan. The appropriate imaging procedures were to be repeated after the third and sixth cycles of treatment. This assessment included clinical evaluation, chest X-ray, CT scan of the abdomen and CA 125 measurement. Once patients were off study a metastatic work-up was repeated every six months for five years or when clinically indicated. It included history, physical examination chest X-ray (or CT scan if indicated), CT scan of the abdomen and laboratory tests of blood including CA 125 measurement.

Study arms. The study regimes were as follows: Control group A: cyclophophamide (700 mg/m^2 *i.v.*) and cisplatin (75 mg/m^2 *i.v.*, at the rate of 1 mg/min). Experimental-therapy group B: paclitaxel (175 mg/m^2 *i.v.*, as a 3-hour continuous infusion) and cisplatin (75 mg/m^2 *i.v.*, at a rate of 1 mg/min). In both groups, courses were repeated every 3 weeks for six cycles, provided the neutrophil count was equal to or more than 100x10^9/L, the platelet count was equal to or more than 100x10^9/L, and toxic effects were not prohibitive. The women assigned to the experimental group were premedicated with dexamethasone 20 mg orally or intravenously 14 and 7 hours before the start of the paclitaxel infusion. Diphenhydramine (50 mg) and any histamine H2 antagonist were administered intravenously 30 minutes before the paclitaxel infusion. Amifostine 910 mg/m^2 was administered as a 15-minute i.v. infusion, prior to chemotherapy in both groups.

The protocol did not include dose escalation. For patients who experienced grade 3 or 4 neutropenia and/or grade 3 or 4 thrombocytopenia a 20% reduction in the paclitaxel or cyclophosphamide dosages was planned, with no reduction in the cisplatin dose. The use of granulocyte colony-stimulating factor was accepted at the investigator's discretion.

Study end points. Before study registration, patients were randomly assigned at each participating Institution. Stratification factors included the treating institution, the FIGO stage (IIB-C, III, or IV), the amount of residual disease (none or microscopic, ≤1 cm, or >1 cm), the performance status and the tumor grade (well differentiated, moderately well differentiated, poorly differentiated not applicable). A total of 128 patients were randomized in the trial.

Patients were assigned to one of the following groups: those who progressed clinically, were stable clinically, those showing partial clinical response or complete clinical response. For those patients undergoing interval debulking surgery, the four groups were progressed surgically, stable surgically, those showing partial surgical response or complete surgical response, pathologically documented. Patients categorized as progressed clinically or surgically finished the protocol treatment and were allowed to receive any second-line treatment at the investigators' discretion. All of the other patients received 3 further cycles of protocol chemotherapy. After six cycles of protocol treatment the final assessment was made as it was done after the third cycle. A reassessment laparotomy was not required to determine the pathological response in patients without measurable disease or measurable disease and complete response. Further management was allowed at the investigators discretion. Patients not showing disease progression at this point could receive three additional cycles of protocol treatment.

Patients in complete remission after five years are followed for life with annual work-up unless symptoms developed.

Progression-free survival (PFS), the primary study end point, was measured from the date of randomization until the date of progression of the disease or death from the disease. Other study end points included clinical response rate, overall survival and quality of life. Overall survival was measured from the date of randomization until the date of death. A complete response (CR) was defined as the disappearance of all clinical evidence of tumor, including normalization of CA 125 level, determined by two observations not less than 4 weeks apart. A partial response (PR) was defined a 50% or greater decrease in the sum of the products of the perpendicular diameters of the measured lesions, determined by two observations not less than 4 weeks apart. No simultaneous increase in the size of any lesion or the appearance of new lesions was permitted. Non-measurable lesions had to remain stable or regress for inclusion in this category. Stable disease was defined as a steady state of response less than a PR or progression less than 25% lasting at least 4 weeks. No new lesions were to appear for inclusion in this category. Progressive disease (PD) was defined as increase of more than 25% in the size of lesions or the appearance of new lesions. A rise in CA 125 alone was not considered to be PD.

Statistical analysis. The primary end point for this study was the comparison of PFS between the treatment groups. The analyses of PFS and overall survival were based on the intent-to-treat policy. (All randomly assigned patients were analyzed according to the arm to which they were assigned). The survival curves were estimated with the use of the Kalplan-Meier method (9). Differences in the time- to-event end points were compared with the use of a two-sided log-rank test. To adjust for confounding covariates, we also estimated the treatment effect by Cox's proportional hazards model (10).

Safety analysis was restricted to the patients who started treatment according to the protocol and for whom at least one cycle of chemotherapy had been documented. Comparisons of proportions between the two arms were done by use of a two-sided chi-squared test or a two-sided Fisher's exact test.

Results

From November 1998 to December 2002, 128 patients with epithelial ovarian cancer were registered onto this study. Eight patients (13%) were ineligible – 6 because their cancer was of an inappropriate stage, 2 because they had different primary tumor. The remaining 120 eligible patients were randomly assigned to either cisplatin-cyclophosphamide group or the cisplatin-paclitaxel group. The characteristics of the eligible patients are listed in Table I.

Of the 120 eligible patients 60 (50%) had clinically measurable disease. The patients were distributed with similar frequency between the treatment groups. The predominant histologic cell type was serous adenocarcinoma (63%), with half of all the patients entering with histologic grade 3 tumors. Median ages were 59 and 57 years for the control and experimental group respectively.

Table I. *Patients' characteristics according to treatment group.*

Characteristic	Cisplatin+ Cyclophosphamide Group A (n=60)	Cisplatin+ Paclitaxel Group B (n=60)
Median age [yr (range)]	59 (30-74)	57(28-75)
WHO PS. No (%)		
0	29 (48.3)	30 (50)
1	29 (30)	18 (30)
2	9 (15)	7 (11.7)
3	4 (6.7)	5 (8.3)
FIGO Stage [No (%)]		
IIB or IIC	15 (25)	14 (23.3)
III	17 (28.3)	18 (30)
IV	28 (46.7)	28 (46.7)
Cell type [No (%)]		
Serous adenocarcinoma	39 (65)	37 (61.6)
Endometriod adenocarcinoma	10 (16.6)	11 (18.4)
Mucinous adenocarcinoma	5 (8.4)	6 (10)
Clear-cell adenocarcinoma	1 (1.6)	2 (3.4)
Other	5 (8.4)	4 (6.6)
Tumor grade [No (%)]		
1: well-differentiated	6 (10)	6 (10)
2: moderately-differentiated	25 (41.6)	24 (40)
3: poorly-differentiated	29 (48.4)	30 (50)

Table II. *Adverse effects per treatment group.*

	Cisplatin+ Cyclophosphamide (n=60)		Paclitaxel+ Cisplatin (n=60)	
	No.	%	No.	%
Neutropenia				
Grade 3	31	51.6	33	55
Grade 4	18	30	21	35
Febrile	0	0	0	0
Thrombocytopenia				
Grade 3	3	5	4	6.6
Grade 4	0	0	0	0
Nausea & vomiting				
Grade 3	15	25	14	23.4
Grade 4	2	3.4	2	3.4
Stomatitis, grade 3	1	1.6	1	1.6
Alopecia, grade 3	12	20	16	26.6
Arthralgia, grade 3	2	3.4	17	28.4
Myalgia, grade 3	1	1.6	15	25
Neurological symptoms				
Grade 3	2	3.4	12	20
Grade 4	0	0	1	1.6
Severe hypersensitivity reactions	0	0	1	1.6

Table III. *Clinical response.*

	Cisplatin+ Cyclophosphamide (n=60)		Paclitaxel+ Cisplatin (n=60)	
	No.	%	No.	%
Complete response (CR)	21	35	23	38.4
Partial response (PR)	14	23.4	16	26.6
Stable disease (SD)	13	21.6	15	25
Progressive disease (PD)	12	20	6	10

Analysis of toxicity has been carried out in 120 patients. The percentages of patients in each treatment group reporting toxicity are listed in Table II. (Common Toxicity criteria, National Cancer Institute, Bethesda). Neutropenia, alopecia, arthralgia and myalgia ($p<0.05$) occurred more frequently among those patients treated with the paclitaxel-containing regimen.

Clinical response was assessed in the 120 patients who were eligible for the study. with clinically or radiologically measurable disease. These results are listed by randomized treatment group in Table III. There was a significant difference ($p<0.05$) in the frequency of response (CR+PR) between treatment groups. Whereas 65% of those on the cisplatin and paclitaxel regimen responded, only 58% of those randomized to cispaltin and cyclophosphamide responded. At the time of statistical analysis, 18 patients (15%), have shown progression of disease, with a significant difference ($p<0.01$) between treatment groups, in favor of paclitaxel containing regimen. Patients in the cyclophosphamide+cisplatin group received paclitaxel at first progression of disease.

The plots of the cumulative proportion of patients surviving progression- free for each of the randomized treatment groups are displayed in Figure 1. The median duration of PFS was 9 months for patients in the CP group and 12 months for patients in the TP group (log-rank $p=0.215$).

Figure 2 depicts the OS for each of the randomized treatment groups. The median durations of survival are 24 months and 20 months for those patients randomized to TP and CP regimen, respectively, (log-rank $p=0.350$). The differences in the overall death rates between treatment groups, adjusted for measurable disease status, performance status, stage, and cell type, may be ascribed to random error ($p=0.234$).

Discussion

Improvements in the systemic chemotherapy of advanced ovarian cancer with associated improvements in survival are relevant to the design of studies testing new regimens and combinations of them (11, 12). Adjunctive chemotherapy

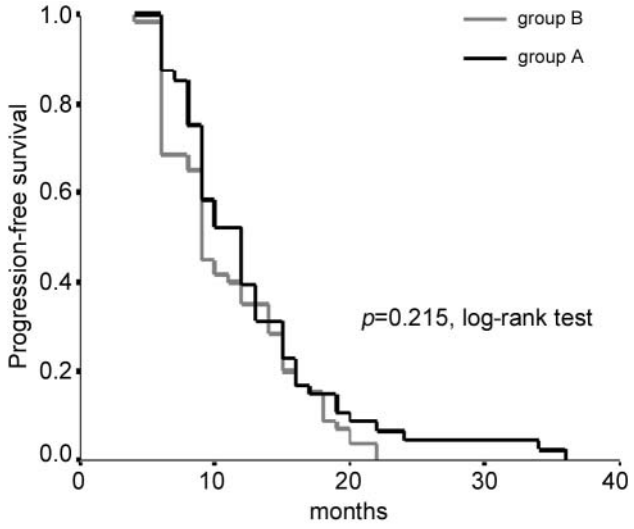

Figure 1. *Progression-free survival according to treatment group.*

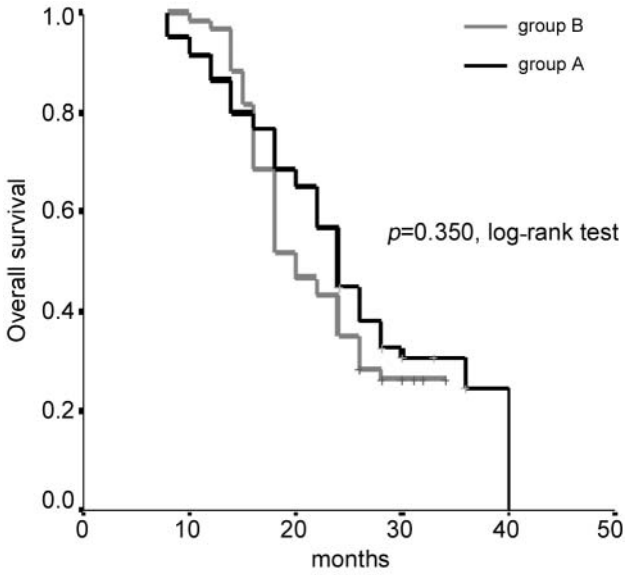

Figure 2. *Overall survival according to treatment group.*

significantly prolongs survival, with most current data supporting the use of platinum- and taxane-based regimes (13, 14). In advanced stage ovarian cancer, two landmark studies (GOG 111 and OV-10) established the superiority of paclitaxel and cisplatin combination over cyclophosphamide and cisplatin regimen (8, 15).

With the equivalence of cisplatin and carboplatin demonstrated in randomized trials, pacilitaxel and carboplatin was considered the gold standard in late 1990s. However, two large randomized trials undertaken primarily to determine if TP offered superior progression-free and overall survival outcomes compared with a standard of CP in women with advanced epithelial ovarian cancer, (GOG 132 and ICON 3) published subsequently, indicated that single agent therapy with either carboplatin or cisplatin was as effective as its combination with paclitaxel (16, 17).

Our results demonstrate that both study chemotherapeutic regimens can be administered safely in almost full doses with acceptable toxicity. In particular the paclitaxel containing regimen appears feasible, with a frequency of response (CR+PR) between treatment groups in favor of paclitaxel. Whereas 65% of those on the cisplatin and paclitaxel regimen responded, only 58% of those randomized to cisplatin and cyclophosphamide responded ($p<0.05$).

Regarding the efficacy, the differences in PFS and OS between the treatments groups in our study did not reach statistical significance. Of course this conclusion should be seen in conjunction with the limitations of the statistical hypothesis used. Possibly larger study size could detect a difference between the two arms. Our results are in accordance with the results of the ICON 3 trial which has also failed to show a survival advantage for the taxane containing arm (16). Similar results have been reported in trials in which a cisplatin regimen was compared with a non platinum regimen in front-line treatment of advanced ovarian cancer patients (17). Another reason that may have affected the true survival between the randomized arms may be the treatments subsequent to the initial assignment. In particular, the early crossover to taxane regimen may have obscured the true survival differences; in terms that paclitaxel as salvage therapy among those randomized to the non paclitaxel regimen may attenuate the OS survival difference if it exists.

Although it may be reasonable to speculate that treatment crossover explain the lack of the differences between the treatment groups, such a conclusion would require a priori assumption that paclitaxel and platinum are effective salvage treatments. In view of the wider availability of paclitaxel at the time this study was conducted, a crossover to paclitaxel was expected to occur more frequently. Nevertheless, it seems that the paclitaxel containing regimen is a feasible treatment for first-line chemotherapy in patients with advanced disease (18, 19). Although paclitaxel efficacy as a salvage treatment has been documented, withholding paclitaxel until clinical progression is an unacceptable option.

In summary, the results from our study do not clearly indicate superiority for the taxane containing arm in terms of overall and progression-free survival. However, cisplatin in combination with paclitaxel yielded superior response rates relative to cisplatin and cyclophosphamide, with an acceptable toxicity profile.

In conclusion, for advanced ovarian cancer, current front-line management should incorporate a taxane with platinum-based therapy. Our results also support the use of a taxane and platinum-based therapy in patients with high-risk early-stage disease.

Issues that remain to be resolved include: the role of intraperitoneal therapy in primary treatment and in persistent disease following primary therapy; the role of maintenance or consolidation treatment with standard chemotherapy or with novel agents following primary therapy; and the optimal use of platinum *vs.* non-platinum agents, and whether used as single agents or in combination, for patients with recurrent disease.

References

1 Randall TC and Rubin SC: Cytoreductive surgery for ovarian cancer. Surg Clin North Am *81*: 871-883, 2001.

2 Gonzalez-Martin AJ: Medical treatment of epithelial ovarian cancer. Expert Rev Anticancer Ther *6*: 1125-1143, 2004.

3 Ozols RF: Update on Gynecologic Oncology Group (GOG) trials in ovarian cancer. Cancer Invest *Suppl 2*: 11-20, 2004.

4 Muggia FM: Recent updates in the clinical use of platinum compounds for the treatment of gynecologic cancers. Semin Oncol, Suppl *14*: 17-24, 2004.

5 Thigpen JT, Blessing JA, Ball H *et al*: Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. J Clin Oncol *12*: 1748-1753, 1994.

6 ICON and EORTC-ACTION investigators: International Collaboration on Ovarian Neoplasm Trial 1 and Adjuvant Chemotherapy in Ovarian Neoplasm Trial: Two parallel randomized phase III trials of adjuvant chemotherapy in patients with early stage ovarian cancer. J Natl Cancer Inst *95*: 105-112, 2003.

7 Mc Guire WP, Hoskins WJ, Brady MF *et al*: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med *334*: 1-6, 1996.

8 Piccart MJ, Bertelsen, James K *et al*: Randomized Intergroup Trial of cisplatin-placlitaxel *versus* cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst *92*: 699-708, 2000.

9 Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.

10 Cox DR: Regression models and life-tables. J R Stat Soc *B34*: 187-202, 1972.

11 Sandercock J, Parmar MK, Torri V *et al*: First-line treatment for advanced ovarian cancer: paclitaxel, platinum and the evidence. Br J Cancer *8*: 815-824, 2002.

12 Harries M and Gore M: Part I: chemotherapy for epithelial ovarian cancer-treatment at first diagnosis. Lancet Oncol *9*: 529-536, 2002.

13 ICON and AGO collaborators: Paclitaxel plus platinum based chemotherapy *versus* conventional platinum based chemotherapy in women with relapsed ovarian cacer: The ICON4/AGO-OVAR 2.2 trial. Lancet *361*: 2099-2106, 2003.

14 Rustin GJ, Timmers P, Nelstrop A *et al*: Comparison of CA-125 and standard definitions of progression of ovarian cancer in the intergroup trial of cisplatin and paclitaxel *versus* cisplatin and cyclophosphamide. Clin Oncol *1*: 45-51, 2006.

15 Stuart G, Bertelsen K, Mangioni C *et al*: Updated analysis shows a highly significant overall survival for cisplatin-paclitaxel as first-line treatment of advanced ovarian cancer: Mature results of the EORTC-NOCOVA-NCI-C and Scottish intergroup trial. Proc Am Soc Clin Oncol *17*: 361A, (abstr 1394), 1998.

16 International Collaborative on Ovarian Neoplasm (ICON) Group: Paclitaxel plus carboplatin *versus* standard chemotherapy with either single agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON 3 randomized trial. Lancet *360*: 505-515, 2002.

17 Muggia FM, Braly PS, Brady MF *et al*: Phase III randomized study of cisplatin *versus* paclitaxel *versus* cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. J Clin Oncol *1*: 106-115, 2000.

18 Ozols RF, Bundy BN, Greer BE *et al*: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol *17*: 3194-3200, 2003.

19 Piccart MJ, Bertelsen K, Stuart G *et al*: Long-term follow-up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide-cisplatin combination in advanced ovarian cancer. Int J Gynecol Cancer *13(Suppl 2)*: 144-148, 2003.

Received June 26, 2006
Revised December 4, 2006
Accepted December 5, 2006