Journal of BUON **17:** 735-739, 2012

ORIGINAL ARTICLE

Maintenance chemotherapy or not in ovarian cancer stages IIIA, B, C, and IV after disease recurrence

G.P. Stathopoulos[1], Ch. Papadimitriou[2], G. Aravantinos[3], S.K. Rigatos[4], N. Malamos[4], J.G. Stathopoulos[1], M. Kaparelou[1], J. Koutantos[1], Ch. Andreadis[5]

[1]First Oncology Clinic, "Errikos Dunant" Hospital; [2]Oncology Department, "Alexandra" Hospital; [3]Oncology Department, "Ag. Anargyri" Cancer Hospital; [4]Oncology Department, "Marika Iliadi" Hospital, Athens; [5]Oncology Department, "Theagenio" Cancer Hospital, Thessaloniki, Greece

Summary

Purpose: *Ovarian cancer may have a high percentage of residual disease after chemotherapy. It is questionable whether second or more lines of chemotherapy are needed in patients with slow-growing residual disease. In the present trial we compared the median survival of patients with residual or recurrent disease who received 1-2 lines of chemotherapy with those who received 3-9 lines.*

Methods: *Two hundred and five patients with advanced stage IIIA, B, C and IV ovarian cancer were divided into two groups based on the number of chemotherapy lines they received. All patients had prior first-line chemotherapy; the criteria for recruitment in the study were: a) residual or recurrent disease and b) failure to respond to first-line therapy. Group A included patients who received 1 or 2 lines of chemotherapy and group B, 3-9 lines.*

Results: *The median survival of group A was 76 months and of group B 53 months ($p<0.001$). Complete response (CR) was observed in 80 out of the 193 (41.45%) evaluable patients, partial response (PR) in 37 (19.17%), stable disease (SD) in 54 (27.98%) and progressive disease (PD) in 22 (11.40%) patients.*

Conclusion: *In ovarian cancer patients with advanced disease, multiple chemotherapy lines (3-9) offer no advantage over 1 or 2 lines, with respect to overall survival.*

Key words: maintenance therapy, ovarian cancer

Introduction

In ovarian cancer patients advanced-stage disease is diagnosed in approximately 60-70% of the cases [1,2]. Initial cytoreductive surgery and first-line systemic chemotherapy may produce an overall response rate in 70-80% of the cases [3,4]. First-line chemotherapy involves cisplatin or carboplatin in combination with paclitaxel, while certain other cytotoxic drugs have been suggested as second-line agents [3,5,6]. These include liposomal doxorubicin, topotecan, docetaxel, gemcitabine and etoposide [6]. Stage III or IV patients who achieve long-lasting complete pathological or clinical remission comprise only 10-15% of the cases [7]. Chemotherapy for residual or recurrent disease could be considered as palliative, since the great majority of patients in this phase are incurable. For these patients, the goals of treatment aim to control the disease-related symptoms and the toxicity of therapy, to improve or maintain a good quality of life and to prolong survival. There are data concerning cytotoxic combinations, the number of cycles and treatment duration [8-12], second-line chemotherapy or salvage treatment, but such data leave the following question unanswered [13-18]: what does one do after second-line chemotherapy while the patient has SD?

There may be a rationale behind continuing the treatment of advanced ovarian cancer with maintenance therapy with one or more combined cytotoxic schedules until disease progression. The main reasons are to ameliorate symptom palliation and to maintain SD by using less active anticancer agents [6]. Disease resistance to chemotherapy and the negative impact on the patient's quality of life would be factors against continuing chemotherapy.

Correspondence to: George P. Stathopoulos, MD, PhD. 2A, Semitelou street, 115 28 Athens, Greece. Tel: + 30 210 7752600, Fax: + 30 210 7251736, E-mail: dr-gps@ath.forthnet.gr

Received 22-05-2012; Accepted 17-06-2012

The present study from 4 different hospitals included mainly stage III but also stage IV ovarian cancer patients with disease recurrence or SD after first-line treatment. On the basis of the number of chemotherapy lines administered, the patients were divided into 2 groups: group A received 1 or 2 lines of chemotherapy and group B 3 or more lines. The selection of cytotoxic schedules was determined by each of the 4 hospitals, but in each case, based on published data. The objectives of the study were to determine and compare overall survival and response rate between the 2 groups.

Methods

Inclusion criteria

Patient eligibility was based on histological confirmation of the diagnosis, and stage determination (stage III, IV), regardless of age. Patients had to have bidimensionally measurable or evaluable disease, World Health Organization (WHO) performance status of 0-2 and life expectancy of at least 3 months. Also, patients were required to have adequate bone marrow reserves (granulocyte count ≥ 1500/dl, platelet count ≥ 120,000/dl), normal renal (serum creatinine < 1.2 mg/dl) and liver function tests (total serum bilirubin < 3 mg/dl, provided that serum transaminases and serum proteins were normal), normal cardiac function with no history of clinically unstable angina pectoris or myocardial infarction or congestive heart failure within the previous 6 months, and no central nervous system involvement.

Exclusion criteria

Patients with active infection, malnutrition or a second primary tumor (except for non-melanoma skin epithelioma or *in situ* cervix carcinoma) were excluded.

All patients had been previously subjected to primary surgery and first-line chemotherapy. Patients who received second or more lines of chemotherapy were a) with residual disease and b) with disease recurrence after CR from first-line chemotherapy.

Evaluation of patients

Patient evaluation included complete medical history and physical examination, full blood count, including leukocyte and platelet counts, a standard biochemical profile (and creatinine clearance when necessary), electrocardiogram, chest x-ray and computed tomography (CT) scans of the chest and upper and lower abdomen. Additional imaging studies were performed upon clinical indication. During the chemotherapy administration period, the patients had a full blood count performed one day before treatment and one week after.

Chemotherapy

Chemotherapy was the main treatment in all of the patients. Taking apart the primary operation, this therapeutic intervention was re-used for cytoreduction in only 20% of the cases with recurrence. All patients had front-line chemotherapy with carboplatin 6 AUC, combined with paclitaxel 175 mg/m^2 every 3 weeks in 75% of the cases, while the remaining 25% received cisplatin 80 mg/m^2, combined with paclitaxel 175 mg/m^2 repeated every 3 weeks for 6-8 cycles. Patients who had no tumor reduction or had SD underwent second-line chemotherapy. Patients who went into CR remained without treatment until recurrence; of the patients with PR, half of them had second-line chemotherapy and the other half remained without treatment until disease progression. Patient evaluation began after disease recurrence or after the failure of first-line chemotherapy. Second-line chemotherapy included 3 main schedules. The chemotherapy combination in disease recurrence was based on cisplatin or carboplatin, taxanes, liposomal anthracycline and topotecan. The second agents given in the combination with one of the above drugs were gemcitabine, vinorelbine, cyclophosphamide or ifosfamide and irinotecan. The schedule mainly included 2 drugs, and only rarely 3. The combinations used are shown in Table 1. The doses were as follows: cisplatin 80 mg/m^2, carboplatin 6 AUC, paclitaxel 175 mg/m^2, liposomal anthracycline 30 mg/m^2, irinotecan 135 mg/m^2, gemcitabine 1000 mg/m^2, topotecan 1.75 mg/m^2 (weekly), vinorelbine 25 mg/m^2 and oxaliplatin 135 mg/m^2. Group A with 96 patients received 1 or 2 lines of chemotherapy (3-6 cycles per schedule) and group B with 97 patients, 3-9 lines.

Definition of response

Imaging-based evaluation was used for the assessment of response. CR was considered to be the disappearance of all measurable/evaluable disease confirmed at 6-8 weeks at the earliest, and PR a 30% decrease of the tumor burden also at 6-8 weeks at the earliest, after completion of 4-6 courses of treatment. In SD neither PR nor PD criteria were met, and in PD a 20% or more increase of tumor burden and no CR, PR, or SD were documented before increased disease. Response data were based on the Response Evaluation Criteria in Solid Tumors (RECIST) [19]. A two-step deterioration in performance status, a >10% loss of weight at pretreatment or increasing symptoms did not by themselves constitute PD, however, the appearance of these complaints was followed by a new evaluation of the extent of disease. Only PR and CR maintained for at least 4 weeks were included and all were confirmed by an independent panel of radiologists.

Trial design/criteria

This was a four-center trial. The primary end-points were to determine the response rate and survival as well as to statistically

Table 1. Cytotoxic agents administered as combination or as monotherapy after disease recurrence

Combination therapies
carboplatin - paclitaxel ± liposomal anthracycline
carboplatin - liposomal anthracycline
carboplatin - cyclophosphamide or ifosfamide
liposomal anthracycline - irinotecan
liposomal anthracycline - gemcitabine
topotecan - paclitaxel
topotecan - gemcitabine
carboplatin - vinorelbine
oxaliplatin - irinotecan
Monotherapy
carboplatin
paclitaxel
topotecan

compare the survival between group A patients who received up to 2 lines of chemotherapy and group B who received 3-9 lines. The time to tumor progression (TTP) was calculated as the treatment-free intervals.

Statistical analysis

Time-to-event analyses were performed and survival distribution was estimated by the Kaplan-Meier curve and the log-rank test for the comparison between the two groups. All reported p-values were two-sided. A p-value of < 0.05 was considered significant. The primary endpoints were to determine overall survival time, response rate and TTP.

Results

Patient characteristics

Two hundred and five patients with advanced stage IIIA, B, C and IV ovarian cancer were recruited between 1997-2008 193 of them (94.15%) were evaluable. The patient characteristics are shown in Table 2. All patients had histologically confirmed epithelial ovarian cancer. Their WHO performance status was 0-2. Metastatic disease was present in the abdominal cavity with ascites and/or omental or peritoneal implants in all patients, and in very few (2%) there were liver or lung-pleura deposits. Forty-four (22.80%) patients were alive at the end of the study. Analyzed were 193 evaluable patients. Twelve (5.85%) of the 205 patients were lost to follow-up.

Table 2. Patient characteristics

Characteristics	*N (%)*
Patients enrolled	205 (100)
Patients evaluated	193 (94.14)
Age, years	
Median	61
Range	34-82
Performance status	
0	30 (15.54)
1	114 (59.07)
2	49 (25.39)
Disease stage	
IIIA	72 (37.31)
IIIB	63 (32.64)
IIIC	46 (23.83)
IV	12 (6.22)
Histology	
Cystadenocarcinoma	179 (92.75)
Endometrioid	14 (7.25)
Lines of chemotherapy	
1-2	96 (49.74)
3-9	97 (50.26)

Compliance with treatment

The total number of courses in the 193 patients was 2266. The number of chemotherapy lines of treatment and the number of patients are shown in Table 3.

The median time interval between each line of treatment varied from 1-36 months. Patients who remained without treatment for 1-3 years still had residual disease in the abdominal cavity but remained symptomless and had a high quality of life.

Response to treatment and survival

CR was observed in 80 (41.45%) out of the 193 evaluable patients, PR in 37 (19.17%), SD in 54 (27.98%) and PD in 22 (11.40%) patients. TTP ranged from 1-36 months (median 12). There was a difference in the number of treatment lines among the 4 participating hospitals (Table 1); 96 patients received 1-2 treatment lines and 97 patients 3-9 lines.

The median survival of group A was 76 months (range 2.5 -179) and of group B it was 53 months (range 3-180; $p<0.001$; Table 4). The Kaplan-Meier estimate of survival is shown in Figure 1.

Table 3. Lines of chemotherapy administered

	Patients, N	*Lines, N*		*Cycles, N*
Group A (1-2 lines)				
	31	1		98
	65	2		484
Total group A	96			582
Group B (3-9 lines)				
	42	3		502
	33	4		523
	10	5		163
	7	6		184
	3	7		161
	1	8		82
	1	9		69
Total group B	97			1684
Total patients	193		Total cycles	2266

Table 4. Patient overall survival

Group	*Patients, N*	*Overall survival (months, median)*	*95% CI*	*Log-rank, p*
A (1-2) lines	96	76	43.2-108.8	
B (3-9) lines	97	53	44.9-61.1	<0.001

95% CI: 95% confidence interval

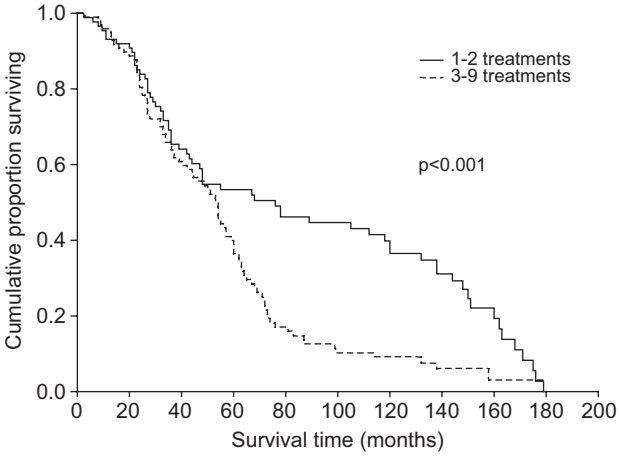

Figure 1. Kaplan-Meier estimate of overall survival.

CA-125 estimation

CA-125 was estimated every 2-3 months or when there was disease progression and was found to be increased in 87.87% of the patients. It varied from 58 to 24,910, fluctuating over time and dropping after treatments. In 12.12% of the patients CA-125 level was normal despite the existence of measurable disease.

Discussion

There is always the question as to whether chemotherapy should be continued by changing cytotoxic agents until disease progression. Arguments for this have been described as improving the situation characterized by a limited number of therapeutic options, providing symptom palliation, maintaining SD status and using newer agents in cases when toxicity is acceptable [6]. However, there are also arguments against treatment until disease progression. These could be the lack of demonstrable benefits, cumulative toxicity and the negative impact on patients' quality of life, as well as psychological issues. The use of more effective agents could be delayed or postponed if there is no disease progression [6].

It is known that the effectiveness of second, third or more chemotherapy lines in almost any malignancy is diminished by resistant cancer cells. This is quite a strong argument for avoiding repeated chemotherapy lines. The concept of consolidation treatment is acceptable and applied as a means to increase the progression-free survival in patients with microscopic or macroscopic residual disease [20]. Second-look laparotomy and consolidation chemotherapy in a slow-growing disease do not seem to be necessary [20]. From the data presented herein, it is indicated that multiple treatments after recurrent stage III or IV disease do not have a major positive effect on survival. It is also shown that after disease recurrence or with residual disease ovarian cancer patients have a long-term survival as indicated by the median survival in this study. Is this due to the application of multiple lines of chemotherapy? The finding that the survival of patients with 3-9 lines of treatment was not statistically longer than that of the patients with 1-2 lines of treatment suggests that the long-term survival is due rather to the slow-growing disease which permits long-term survival with SD status. This is shown by the 64% of our patients whose disease, even after multiple treatment lines, remained in a stable condition. Cytoreductive surgery usually has no place in the treatment of abdomino-pelvic recurrent ovarian cancer with the exception of the necessary surgical correction of intestinal or urinary obstruction [21]. Careful selection of a treatment strategy is needed when repetition of chemotherapy is considered. New agents with low toxicity could be a choice. There are data for second-line treatment choices [17,22-25], however, for third, fourth or more lines of treatment no convincing data over their effectiveness exist. More randomized studies comparing whether to treat or not after certain chemotherapy schedules may be beneficial. A randomized study used two different schedules of chemotherapy in patients with disease recurrence after CR to first-line chemotherapy with a cisplatin-based regimen and after a progression-free interval of more than 12 months [26]. Further treatment (second- or third-line) is presented in non-responding patients in a crossover treatment (group A paclitaxel, group B cisplatin-doxorubicin-cyclophosphamide). It was reported that 17% and 30% of the patients, respectively, achieved CR and 28% and 25%, respectively had a partial response. The median survival time was 25.8 and 34.7 months, respectively [26]. This study, like ours, indicated long survival benefit of patients after disease recurrence.

Our study indicates that after second-line chemotherapy the majority of patients with SD experienced no additional amelioration by any further chemotherapy. Thus, maintenance treatment (third, fourth or more lines) is not of any value.

References

1. Fishman DA, Schwartz PE. Current approaches to diagnosis and treatment of ovarian germ cell malignancies. Curr Opin Obstet Gynecol 1994; 6: 98-104.
2. Jemal A, Tiwari RC, Murray T et al. Cancer statistics 2004. CA Cancer J Clin 2004; 54: 8-29.
3. 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 2003; 21: 3194-3200.
4. Bookman MA, McGuire WP III, Kilpatrick D et al. Carboplatin and paclitaxel in ovarian carcinoma: a phase I study of the Gynecologic Oncology Group. J Clin Oncol 1996; 14: 1895-1902.
5. McGuire 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 1996; 334: 1-6.
6. Ozols RF, Schwartz PE, Eifel PJ. Ovarian cancer, fallopian tube carcinoma, and peritoneal carcinoma. In: DeVita VT Jr, Hellman S, Rosenberg SA (Eds): Cancer: principles and practice of oncology. Lippincott Williams and Wilkins, Philadelphia 2001, pp 1597-1632.
7. Herzog TJ. Recurrent ovarian cancer: how important is it to treat to disease progression? Clin Cancer Res 2004; 10: 7439-7449.
8. Hakes TB, Chalas E, Hoskins WJ et al. Randomized prospective trial of 5 versus 10 cycles of cyclophosphamide, doxorubicin, and cisplatin in advanced ovarian carcinoma. Gynecol Oncol 1992; 45: 284-289.
9. Gershenson DM, Mitchell MF, Atkinson N et al. The effect of prolonged cisplatin-based chemotherapy on progression-free survival in patients with optimal epithelial cancer: "maintenance" therapy reconsidered. Gynecol Oncol 1992; 47: 7-13.
10. Cesano A, Lane SR, Poulin R, Ross G, Fiels SZ. Stabilization of disease as a useful predictor of survival following second-line chemotherapy in small cell lung cancer and ovarian cancer patients. Int J Oncol 1999; 15: 1233-1238.
11. Möbus V, Pfall PN, Volm T, Kreinberg R, Kanbitzschs J. Long time therapy with topotecan in patients with recurrence of ovarian carcinoma. Anticancer Res 2001; 21: 3551-3446.
12. Von Gruenigen VE, Karlen JR, Waggoner SE. A case of chronic paclitaxel administration in ovarian cancer. Gynecol Oncol 2003; 89: 532-535.
13. Kudelka AP, Tresukosol D, Edwards CL et al. Phase III study of intravenous topotecan as a 5-day infusion for refractory epithelial ovarian carcinoma. J Clin Oncol 1996; 14: 1552-1557.
14. Creemers GJ, Bolis G, Gore M et al. Topotecan: an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European Phase II study. J Clin Oncol 1996; 14: 3056-3061.
15. ten Bokkel Huinink W, Gore M, Carmichael J et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997; 15: 2183-2193.
16. McGuire WP, Blessing JA, Bookman MA, Lentz SS, Dunton CJ. Topotecan has substantial antitumor activity as a first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2000; 18: 1062-1067.
17. Gordon AN, Fleagle JT, Guthrie D et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001; 19: 3312-3322.
18. Dizon DS, Hensley ML, Poynor EA et al. Retrospective analysis of carboplatin and paclitaxel as initial second-line therapy for recurrent epithelial ovarian carcinoma: application towards a dynamic disease state model of ovarian cancer. J Clin Oncol 2002; 20: 1238-1247.
19. Therasse P, Arbuck SG, Eisenhower EA et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92: 205-216.
20. Gonzalez-Martin AJ. Medical treatment of epithelial ovarian cancer. Expert Rev Anticancer Ther 2004; 4: 1125-1143.
21. Salzberg M, Thürlimann B, Bonnfois H et al. Current concepts of treatment strategies in advanced or recurrent ovarian cancer. Oncology 2005; 68: 293-298.
22. Partidge EE, Phillips JL, Menck HR. The National Cancer Data Base report on ovarian cancer treatment in United States hospitals. Cancer 1996; 78: 2236-2246.
23. Ozols RF, Markham M, Thigpen JT. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin and cisplatin in women with ovarian cancer: the ICON3 randomized trial. Lancet 2002; 360: 505-515.
24. Freidlander M, Millward MJ, Bell D et al. A phase II study of gemcitabine in platinum pretreated patients with advanced epithelial ovarian cancer. Ann Oncol 1998; 9: 1343-1345.
25. Allen DG, Heintz AP, Touw FW. A meta-analysis of residual disease and survival in stage III and IV carcinoma of the ovary. Eur J Gynaecol Oncol 1995; 16: 349-356.
26. Cantu MG, Buda A, Parma G et al. Randomized controlled trial of single-agent paclitaxel versus cyclophosphamide, doxorubicin, and cisplatin in patients with recurrent ovarian cancer who responded to first-line platinum-based regimens. J Clin Oncol 2002; 20: 1232-1237.