Long-term results from a phase II study of paclitaxel combined with doxorubicin in recurrent platinum refractory ovarian cancer

C. Tropé, G. Kristensen, J. Kisic, J. Kaern

Department of Gynecologic Oncology, The Norwegian Radium Hospital, Montebello, Oslo (Norway)

Summary

Background: There is still a need for newer non-cross-resistant agents and combinations to be tried in cases of failure after first line platinum-based therapy. Several agents have demonstrated activity after failure of platinum-containing regimens. Response rate in true platinum refractory disease up to 20% but with poor long-term survival, has been reported by single drug paclitaxel. In an effort to improve response rate and survival duration obtainable with single drug paclitaxel, we have combined paclitaxel with doxorubicin for the treatment of patients refractory to cisplatin-cyclophosphamide.

Patients and methods: Between October 1994 and November 1996, 23 patients whereof 21 refractory to cisplatin-cyclophosphamide were enrolled for toxicity and survival analysis after recieving the combination doxorubicin 50 mg/m2 and paclitaxel 135 mg/m^2 every third week for four courses. Responding patients continued on single drug paclitaxel 175 mg/m^2 every third week until unacceptable toxicity or tumor progression occurred.

Results: The objective response rate (CR + PR) was 33%, 95% CI (14.6-57). The median duration of response was 8.5 months (range 4.0-62.5+) and the median overall survival was 15.5 months (range 4.0-63.5+). No serious toxicity was registered.

Conclusion: Doxorubicin combined with paclitaxel could safely be administered using this schedule. This study shows that some patients obtaining CR can be rendered disease-free for a substantial period of time, sometimes five years or more. A median overall survival of 15.5 months with a 5-year survival probability of 15% is impressive. However, although responses can be induced in a significant number of patients, the survival figures remain poor.

Key words: Cisplatin refractory ovarian cancer; Paclitaxel; Doxorubicin; Second-line treatment.

Introduction

Before the results of GOG111 [1] and the reconfirmating study OV10 [2] the standard treatment in advanced ovarian cancer in our institution was cyclophosphamide combined with cisplatin. Unfortunately, the majority of these women with advanced ovarian cancer, even those with surgically defined as complete response, will ultimately have recurrent disease and die of consequences of progressive cancer [3]. Thus, there is a need for second-line treatment of patients with recurrent ovarian cancer. Several agents have demonstrated activity after failure of a cisplatin containing regimen. Until recently there was no agent that significantly improved survival for patients with platinum-resistant disease [3]. Therefore, there is still a need for newer, non-cross-resistant agents and combinations to be tried in cases of failure after front-line platinum-based therapy. McGuire *et al.* [4] reported a 25% response rate of single agent paclitaxel in patients with persistent or refractory epithelial ovarian cancer. Since then several phase II studies of paclitaxel monotherapy have been conducted and an overall response rate of 20-48% has been achieved in the treatment of advanced ovarian cancer cases that relapsed after or during previous platinum-based therapy (3).

Doxorubicin has shown activity in early trials against epithelial ovarian cancer, both as upfront treatment and as second-line treatment [5, 6]. Several trials have compared standard treatment alkylating agents and platinum therapy with and without the addition of doxorubicin. Recently a metanalysis of these randomized trials was able to show a significant improvement in survival (7%) in doxorubicin-containing arms [7, 8]. Later two other metanalyses showed the same survival benefit for platinum-anthracycline-based combinations [5, 9]. The same results – that doxorubicin adds efficacy and not only toxicity to the old standard treatment – have been obtained in Sweden [10].

With few notable exceptions, second-line treatment of patients with ovarian cancer has yielded disappointing results. The majority of patients with recurrent refractory ovarian cancer still fail to have an objective response to salvage chemotherapy with single agent paclitaxel. Furthermore, 5-year survival, even among responders to paclitaxel, remains unacceptably poor [11, 12]. Therefore, one option for achieving further progress in second-line treatment in recurrent platinum refractory ovarian cancer might be the addition of a non-cross resistant drug to platinum. Both doxorubicin and its analogues have shown activity in second-line treatment in platinum and paclitaxel refractory ovarian cancer [13-15], and we agree with duBois *et al.* [16], that anthracyclines are among the candidates to choose in combination with paclitaxel in platinum refractory recurrent ovarian cancer.

In an effort to improve the response rate and survival duration obtainable with single-drug paclitaxel, we have combined paclitaxel with doxorubicin for the treatment of patients refractory to cisplatin-cyclophosphamide.

Revised manuscript accepted for publication January 20, 2001

Patients and Methods

Twenty-three patients with recurrent ovarian cancer, whereof 21 refractory to platinum were enrolled in this phase II study from October 1994 to November 1996. Patient characteristics are shown in Table 1. Standard eligibility criteria for phase II studies performed in this patient population were used. The patients were required to have histologically proven recurrent epithelial ovarian cancer with measurable disease defined as bidimensional lesions with clearly defined margins on MRI or CT scan with a diameter of ≥ 0.5 cm or palpable lesion with both diameters ≥ 2 cm. Platinum refractory disease was defined as relapse or progression during or within six months from the last given platinum treatment. The majority of patients were recruited from those patients who were refractory to cyclophosphamide-cisplatin in our control arm in the OV10 study [2].

The interval between the last dose of the prior platinum regimen and start of doxorubicin combined with paclitaxel was 2.0 months (range 1-4). Median follow-up was 15.5 months (range 4.0-63).

The left ventricle ejection fraction (LVEF) as evaluated by multigated isotope cardiography (MUGA) had to be with in normal limits (50% or more).

Study treatment

Doxorubicin (Adriamycin®) 50 mg/m² was dissolved in 250 ml of isotone glucose and administered as a short infusion (approximately 30 minutes), followed 30 minutes later by paclitaxel (Taxol®) 135 mg/m² infused over three hours preceded by standard anti-allergic medication every third week for four courses. Responding patients (complete response = CR and partial response = PR) and patients with stable disease (SD) continued on single paclitaxel 175 mg/m² 3-hour infusion every three weeks until unacceptable toxicity or tumor progression occurred.

Patients given two or more courses were evaluable for response and toxicity. Decisions whether or not to continue treatment with doxorubicin-paclitaxel were made on the basis of tumor reassessment every 3rd cycle. Patients with disease progression (PD) went off study treatment.

Table 1. — *Patient characteristics at start of doxorubicin-paclitaxel (AT).*

Number of patients entered	23
Number of eligible	21
Median age	50 (range 32-63)
FIGO stage at primary diagnosis	
I	2
II	–
III a	1
III b	3
III c	11
IV	4
Histologic type	
Serous	19
Endometrioid	1
Unclassifed adenocarcinoma	1
Histologic grade	
Highly differentiated	4
Moderately differentiated	8
Poorly differentiated	8
Not graded	1
Size of lesion at the start of AT	
< 2 cm	1
2-5 cm	11
> 5 cm	9
Localization of recurrent disease at the start of AT	
Pelvic	9
Abdomen	7
Abdomen + distant	5
Treatment lines before AT	
1 Cyclophosphamide + cisplatin	17
2 Cisplatin + paclitaxel	2
3 Cisplatin	2
Platinum-resistant disease	21
Platinum-sensitive disease	2

Toxicity and efficacy evaluation

Hematologic screening was performed at base-line and then at the 15th and 21st day in cycles during the treatment period and blood chemistry (serum creatinine, alkaline phosphates, bilirubin, and liver enzymes) were measured at base-line and prior to each course.

Electrocardiography (ECG) and MUGA scans were done before treatment and initially after a cumulative doxorubicin dose of 200 mg/m². When paclitaxel was continued as a single drug, a MUGA scan was performed before the first and the fourth course. Patients were also monitored at the end of therapy.

Performance status (WHO) was assessed at baseline and at the start of every treatment cycle. Subjectively toxicity (WHO) was recorded at the start of every new cycle.

Tumor evaluations were performed at baseline and at every 3rd week by means of physical examinations and appropriate radiological investigations. The image techniques used at base-line to measure a given tumor lesion were repeated throughout the study period. Tumor response was graded in accordance with the WHO response criteria [17].

Progression free survival (PFS) was calculated from the first day of study treatment to the day of documented PD or censored observation. Response duration of patients who obtained CR and PR was calculated from the day of first observation of response to the day of documented PD or censored observation. Overall survival was calculated from the first day of the study treatment to death or censored observation. The follow-up closed the last of August 2000.

Survival distribution was estimated by the Kaplan-Meier method. Toxicity was tabulated.

Results

Out at 23 patients, 17 patients previously treated with cyclophosphamide and cisplatin entered the trial. All 23 patients were eligible for toxicity and 21 patients were eligible for response evaluation (2 patients had platinum sensitive disease at the start of doxorubicin-paclitaxel and were therefore excluded in the final analysis).

Treatment compliance

Prior chemotherapy regimens and number of treatment lines before doxorubicin-paclitaxel are shown in Table 1. At the time of analysis (1, September 2000) a total of 136 courses (73 doxorubicin-paclitaxel and 63 paclitaxel) had been given to the 21 eligible patients. All the responding patients received the calculated cumulative doxorubicin dose of 200 mg/m². The median number of courses was

Table 2. — *Clinical response rate, response duration, progression free survival (PFS) and overall survival to paclitaxel-doxorubicin in eligible platinum refractory patients (n=21).*

	No of patients	%	Median response duration months	range	Median PFS months	range	Median survival months	range
Complete response	3	14	38.0	(5.0-62.5+)	41	(7-63.5+)	59+	(53+-63.5+)
Partial response	4	19	8.0	(4.0-11.0)	11	(6.5-16.5)	22.5	(13.5-30.5)
Stable disease	9	43	6.0	(3.0-9.5)	7	(3.0-10.5)	14.5	(4.0-30.0)
Progressive disease	5	24	–		2.0	(1.5-3.5)	14.0	(4.0-37.5)
Complete + partial response	7	33	8.5	(4.0-62.5+)	11.0	(6.5-63.5+)	30.5	(13.5-63.5+)

eight (range 2-18). Seven courses were postponed one week due to neutropenia and one course due to urinary infection. No dose reduction was performed.

Clinical response evaluation

Table 2 shows the clinical response rate, response duration, PFS and overall survival. The objective response rate was 33%, 95% CI (14.6-57). There was no correlation between age, primary stage, histology, histologic grade, tumor size, and number of recurrent lesions or localization of recurrent disease, previous response rates and previous duration of response with response rate to doxorubicin-paclitaxel.

Response duration and time to progression

The median duration of response was 8.5 months (range 4.0-62.5+). The PFS survival curve for all patients is shown in Figure 1. Patients who obtained CR and PR had significantly longer PFS than those who did not (p = 0.02). Details for response duration and PFS are shown in Table 2.

Survival

The median overall survival was 15.5 months (range 4.0-63.5+) (Figure 2).

The patients who obtained CR or PR had significantly longer overall survival than those who did not (p = 0.01).

Toxicity

Toxicity data based on the total group are shown in Table 3. There were no treatment-related deaths. All patients experienced grade 3 alopecia. Grade 3-4 neutropenia was experienced in 18% of all courses, but only

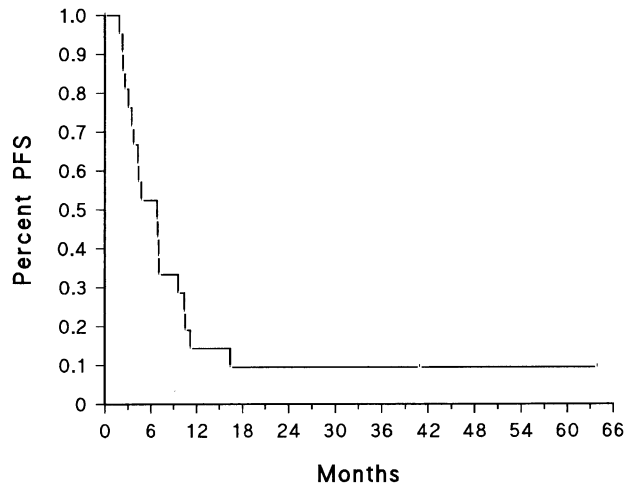

Figure 1. — Progression-free survival (PFS) curve of 21 patients with platinum-resistant recurrent ovarian cancer treated with the combination of paclitaxel and doxorubicin.

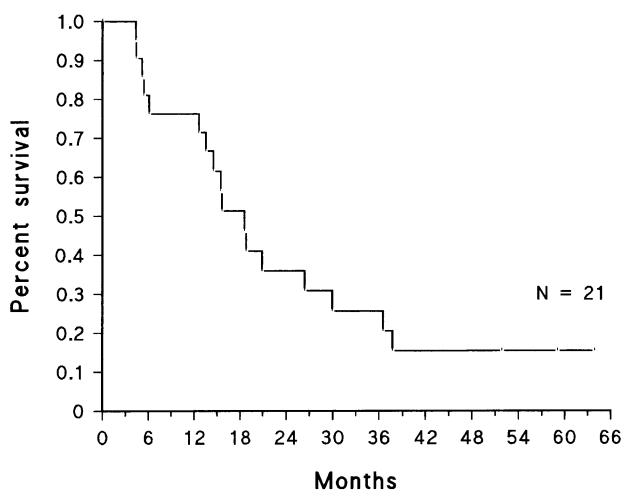

Figure 2. — Overall survival curve of 21 patients with platinum resistant recurrent ovarian cancer treated with the combination of paclitaxel and doxorubicin.

Table 3. — *Toxicity according to WHO grading (n=23).*

WHO grade	0	1	2	3	4
Anemia	22	1	–	–	–
Neutropenia	17	–	2	2	2
Thrombocytopenia	22	–	–	1	–
Infection-fever	19	1	–	3	–
Nausea-vomiting	22	1	–	–	–
Myalgia	15	8	–	–	–
Arthralgia	16	7	–	–	–
Cardiotoxicity	22	–	–	1	–
Neurotoxicity	21	2	–	–	–
Alopecia	–	–	–	23	–

No other toxicity was registered.

three patients had febrile neutropenia. Myalgia or arthralgia grade 1 was noted in eight and seven patients, respectively. No severe neuro-toxicity, nail-toxicity or hypersensitive reactions were observed.

No changes in LVEF were registered and no patients developed congestive heart failure (CHF). Twelve patients continued with paclitaxel as single-drug therapy

following cessation of doxorubicin (after 4 planned doxorubicin-paclitaxel courses) and LVEF was monitored in all of them with no observed pathology. No extra days of hospitalization due to toxicity were needed.

Discussion

This study was designed to investigate the objective response rate in a phase II setting, but we also wanted to address two important questions regarding 1) if doxorubicin-paclitaxel in this setting has a significant impact on long-term survival. 2) Evaluating the safety of a short (3-hour) infusion of paclitaxel when given with premedication and combined with doxorubicin.

The clinical classification of platinum refractory disease used in this study is an adoption of those proposed by Markman [18] and Thigpen [19].

In this study, there was an overall response rate of 33%, 95% CI (14.6-57) in 21 patients with recurrent platinum refractory ovarian cancer. This is of particular interest as the patients, besides platinum refractory disease also had quite extensive disease. It is difficult to make a direct comparison of response rates across non-randomized phase II studies, but the high response rate achieved in our study is better than that achieved with topotecan (13.7%) [20] oral etoposide (26.8%) [21], gemcitabine (13%) [22] and liposomal doxorubicin (18.3%) [23] in the same platinum refractory patient population. However, in the liposomal doxorubicin study the patient population was also refractory to paclitaxel [23]. Our findings are similar to those of Goldberg *et al.* [12] and Johnston *et al.* [24] who reported an objective response rate of about 28% with paclitaxel combined with cisplatin in platinum and paclitaxel refractory patients.

Median duration of response and median PFS was 8.5 months (range 4.0-62.5+) and 7.0 months (range 1.8-63.5+) which are better than those reported for topotecan, 4.5 and 3 months, respectively [20] and for etoposide 4 and 5.5 months, respectively [21] and for liposomal doxorubicin 6 months and 5.5 months, respectively [23]. This is also better than we had achieved at our institution with single-drug hexamethylmelamine, paclitaxel, etoposide and tamoxifen [3] and in two randomized studies including paclitaxel in the same patient population [25, 26].

The combination of doxorubicin and paclitaxel has been evaluated in advanced breast cancer in several phase I and II studies [27, 28] Gehl *et al.* showed that this combination is highly active, but is accompanied by the dose-limiting toxic effects of neutropenia, nephropathy and cardiac toxicity [28]. The median cumulative dose of doxorubicin with which CHF occurred was 392 mg/m^2 (range 329-550 mg/m^2). In the Gianni study [29] 21% of the patients developed CHF after a median 480 mg/m^2. According to Gehl *et al.* [28] this regimen can be continued in its present form if doxorubicin is stopped at 360 mg /m^2. When our study was designed, we were aware of the synergy between doxorubicin and paclitaxel, therefore, we lowered the dose of doxorubicin to 50 mg/m^2 and the maximum cumulative dose to 200 mg/m^2. About the same time as our study, Kurtz *et al.* [30] evaluated the feasibility of doxorubicin/epirubicin plus paclitaxel combination therapy for recurrent advanced ovarian cancer in a pilot study of 24 patients. Both platinum sensitive and platinum refractory patients were included. Twenty-four patients received 150 mg/m^2 paclitaxel on day one with either 50 mg/m^2 doxorubicin on day one or 75 mg/m^2 epirubicin on day one every three weeks. A 27% overall response rate was obtained. No difference was observed between patients treated with doxorubicin and those treated with epirubicin. The median duration of response was 2.8 months and the median overall survival was ten months, which is inferior to our combination. In their study there was, like in our study, no evidence of myocardial toxicity or allergic reactions. Interestingly, we did not observe adverse effects from continuing paclitaxel as a single agent following combination therapy, which is in accordance with data from Gianni *et al.* [29] in breast cancer. Overall toxicity of the study was manageable. There was no treatment related or serious morbidity. No patient failed to complete the study due to either myelotoxicity or neurotoxicity.

Our study shows that some patients obtaining CR can be rendered disease-free for a substantial period of time, sometimes five years or more. A median survival of the whole group of 15.5 months (range 4.0-63.5+) with a 5-year survival probability of 15% is impressive. While the benefit of treatment with combination doxorubicin and paclitaxel over single-agent paclitaxel alone in salvage therapy for recurrent platinum refractory ovarian carcinoma is unclear and cannot be proven in the absence of a randomized clinical trial, our findings do indeed suggest a possible benefit and would support undertaking such a trial.

Only one randomized phase II study favoring the use of platinum-based combination (cyclophosphamide, adriamycin and cisplatin) over single-agent paclitaxel has so far been published, but this study by Colombo *et al.* [31] has been presented only in abstract form and their patients had platinum-sensitive disease.

References

[1] McGuire W. P., Hoskins W. J., Brady M. F., Kucera P. R., Partridge E. E., Look K. Y., D. L., Davidson M.: "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), 1.

[2] Piccart M. J., Bertelsen K., James K., Cassidy J., Mangioni C., Simonsen E. *et al.*: "Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results". *J. Natl. Cancer Inst.*, 2000, *92* (9), 699.

[3] Trope C., Kristensen G.: "Current status of chemotherapy in gynecologic cancer". *Semin. Oncol.*, 1997, *24* (5 Suppl. 15), S15.

[4] McGuire W. P., Rowinsky E. K., Rosenshein N. B., Grumbine F. C., Ettinger D. S., Armstrong D. K., Donehower R. C.: "Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms". *Ann. Intern. Med.*, 1989, *111* (4), 273.

[5] A'Hern R. P., Gore M. E.: "Impact of doxorubicin on survival in advanced ovarian cancer". *J. Clin. Oncol.*, 1995, *13* (3), 726.

[6] Vermorken J. B., Harper P. G., Buyse M.: "The role of anthracyclines in epithelial ovarian cancer". *Ann. Oncol.*, 1999, *10* (Suppl. 1), 43.

[7] Ovarian Cancer Meta-Analysis Project: "Cyclophosphamide, doxorubicin, and cisplatin chemotherapy for ovarian carcinoma: A metanalysis". *J. Clin. Oncol.,* 1991, *9*, 1668.
[8] Stuart G., Bertelsen K., Mangioni C. *et al.*: "Updated analysis shows a highly significant improved overall survival for cisplatin-paclitaxel as first-line treatment of advanced ovarian cancer: Mature results of the EORTC-GCCG, NOCOVA, NCIC CTG and Scottish Intergroup Trial". *Proc. Am. Soc. Clin. Oncol.*, 1998, *17*, 361.
[9] Fanning J., Benner T. Z., Hilgers R. D.: "Meta-analysis of cisplatin doxorubicin, and cyclophosphamide vs. cisplatin and cyclophosphamide chemotherapy of ovarian carcinoma". *Obstet. Gynecol.*, 1992, *80*, 954.
[10] Trope C., Andersson H., Bjorkholm E., Frankendal B., Himmelman A., Hogberg T. *et al.*: "Doxorubicin-melphalan with and without cisplatin in advanced ovarian cancer-ten-year survival results from a prospective randomized study by the Swedish Cooperative Ovarian Cancer Study Group". *Acta Oncol.*, 1996, *35* Suppl. 8, 109.
[11] Trope C., Hogberg T., Kaern J., Bertelsen K., Bjorkholm E., Boman K. *et al.*: "Long-term results from a phase II study of single agent paclitaxel (Taxol) in previously platinum treated patients with advanced ovarian cancer: the Nordic experience". *Ann. Oncol.*, 1998, *9* (12), 1301.
[12] Goldberg J. M., Piver M. S., Hempling R. E., Recio F. O.: "Paclitaxel and cisplatin combination chemotherapy in recurrent epithelial ovarian cancer". *Gynecol. Oncol.*, 1996, *63* (3), 312.
[13] Vermorken J. B., Kobierska A., van-der-Burg M. E., Chevallier B., Zanaboni F., ten-Bokkel-Huinink W. W. *et al.*: "High-dose epirubicin in platinum-pretreated patients with ovarian carcinoma: the EORTC-GCCG experience". *Eur. J. Gynaecol. Oncol.*, 1995, *16* (6), 433.
[14] Havsteen H., Bertelsen K., Gadeberg C. C. *et al.*: "A phase II study with epirubicin as second-line treatment of patients with advanced epithelial ovarian cancer". *Gynecol. Oncol.*, 1996, *63*, 210.
[15] Vermorken J. B., Kobierska A., Chevallier B., Zanaboni F., Pawinski A., Bolis G. for the EORTC Gynecological Cancer Cooperative group: "A phase II study of high-dose epirubicin in ovarian cancer patients previously treated with cisplatin". *Ann. Oncol.*, 2000, *11*, 1035.
[16] du Bois, Luck H. J., Bauknecht T., Meier W., Richter B., Kuhn W. *et al.*: "First-line chemotherapy with epirubicin, paclitaxel, and carboplatin for advanced ovarian cancer: a phase I/II study of the Arbeitsgemeinschaft Gynakologische Onkologie Ovarian Cancer Study Group". *J. Clin. Oncol.*, 1999, *17* (1), 46.
[17] World Health Organization. Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No 48. Geneav, WHO 1979.
[18] Markman M., Hoskins W.: "Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated population [editorial; comment]". *J. Clin. Oncol.*, 1992, *10* (4), 513.
[19] Thigpen J. T., Vance R. B., Khansur T.: "Second-line chemotherapy for recurrent carcinoma of the ovary". *Cancer*, 1993, *71* (4 Suppl.), 1559.
[20] Bookman M. A., Malmstrom H., Bolis G., Gordon A., Lissoni A., Krebs J. B., Fields S. Z.: "Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel". *J. Clin. Oncol.*, 1998, *16* (10), 3345.
[21] Rose P. G., Blessing J. A., Soper J. T., Barter J. F.: "Prolonged oral etoposide in recurrent or advanced leiomyosarcoma of the uterus: a gynecologic oncology group study". *Gynecol. Oncol.*, 1998, *70* (2), 267.
[22] Shapiro J. D., Millward M. J., Rischin D., Michael M., Walcher V., Francis P. A., Toner G. C.: "Activity of gemcitabine in patients with advanced ovarian cancer: responses seen following platinum and paclitaxel". *Gynecol. Oncol.*, 1996, *63* (1), 89.
[23] Gordon A. N., Granai C. O., Rose P. G., Hainsworth J., Lopez A., Weissman C. *et al.*: "Phase II Study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer". *J. Clin. Oncol.*, 2000, *18*, 3093.
[24] Johnston C. M., Pearl M. L., Reynolds R. K., Roberts J. A., Morley G. W.: "Treatment of refractory ovarian carcinoma with paclitaxel and cisplatin after treatment failure with single-agent paclitaxel". *Eur. J. Gynaecol. Oncol.*, 1995, *16*, 439.
[25] Eisenhauer E. A., ten-Bokkel-Huinink W. W., Swenerton K. D., Gianni L., Myles J., van-der-Burg M. E. *et al.*: "European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion". *J. Clin. Oncol.*, 1994, *12* (12), 2654.
[26] ten-Bokkel H. W., Gore M., Carmichael J., Gordon A., Malfetano J., Hudson I. *et al.*: "Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer [see comments]". *J. Clin. Oncol.*, 1997, *15* (6), 2183.
[27] Conte P. F., Gennari A.: "Anthracyclines-paclitaxel combinations in the treatment of breast cancer". *Ann. Oncol.*, 1997, *8* (10), 939.
[28] Gehl J., Boesgaard M., Paaske T., Vittrup J. B., Dombernowsky P.: "Combined doxorubicin and paclitaxel in advanced breast cancer: effective and cardiotoxic". *Ann. Oncol.*, 1996, *7* (7), 687.
[29] Gianni L., Munzone E., Capri G. *et al.*: "Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: High antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study". *J. Clin. Oncol.*, 1995, *13*, 2688.
[30] Kurtz J. E., Deplanque G., Duclos B., Eichler F., Giron C., Limacher J. M. *et al.*: "Paclitaxel-anthracycline combination chemotherapy in relapsing advanced ovarian cancer after platinum-based chemotherapy: a pilot study". *Gynecol. Oncol.*, 1998, *70* (3), 414.
[31] Colombo N., Marzola M., Parma G. *et al.*: "Paclitaxel vs CAP (cyclophosphamide, adriamycin, cisplatin) in recurrent platinum sensitive ovarian cancer: A randomized phase II study (Abstract)". *Proc. Am. Soc. Clin. Oncol.*, 1996, *15*, 751a.

Address reprint requests to:
CLAES G. TROPÉ, MD. Ph.D.
Dept. of Gynecologic Oncology
The Norwegian Radium Hospital
Montebello, N-0310 Oslo (Norway)