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Original Paper

Ten-year Results of a Randomised Trial Comparing Cisplatin with Cisplatin and Cyclophosphamide in Advanced, Suboptimally Debulked Ovarian Cancer

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176 eligible patients with advanced suboptimally operated ovarian carcinoma were randomly allocated to receive either cisplatin 75 mg/m^2 or cisplatin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (CP) every 28 days for six courses. The overall clinical response rates (complete response plus partial response) were 52 and 63% for CP and cisplatin, respectively (non-significant). Including results obtained by second-look laparotomy, we did not observe a statistically significant difference in response rates in the two treatment groups. Median progression-free survival was 10 and 11.9 months for CP and cisplatin, respectively (non-significant). No significant difference was observed in overall survival, with a median of 19.4 and 21.5 months for CP and cisplatin, respectively. Thirty-seven platinum-resistant and 27 platinum-sensitive tumours were treated with carboplatin or cisplatin as second-line therapy. Response rates to platinum second-line therapy were 6 and 50% for resistant and sensitive tumours, respectively ($P < 0.001$). This difference in response rate was also confirmed by survival analysis. Patients with platinum-sensitive tumours survived longer when they were treated with platinum-containing chemotherapy ($P = 0.005$). Median survival was 22.8 and 8.5 months after initiation of second-line treatment for the platinum-containing and platinum-free regimens, respectively. In summary, we observed in suboptimally operated ovarian carcinoma patients similar response rates, progression-free interval, and overall survival for equitoxic cisplatin and CP. However, the doses of cisplatin and cyclophosphamide chosen were substantially lower than current standard doses of CP. Our study demonstrates, therefore, that a suboptimal dose of CP is as effective as optimal dose monotherapy cisplatin. Patients with recurrences considered as platinum-sensitive had a significantly higher response rate and improved survival when retreated with platinum-containing therapy.

Key words: ovarian neoplasms, drug therapy, cisplatin, cyclophosphamide, cisplatin sensitivity
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INTRODUCTION

IN RECENT years, there has been intense interest in the chemotherapy of ovarian carcinoma, and several large-scale, randomised trials of various drug combinations have been conducted [1]. Initially, alkylating agents were applied, but a combination of doxorubicin with melphalan has been shown to be superior to the alkylating agent alone [2]. Since cisplatin was introduced as single-agent treatment in patients with advanced epithelial ovarian cancer, several studies have demonstrated improved survival using this drug. We have demonstrated that cisplatin is superior to thiotepa in inducing response in ovarian carcinoma patients (66% versus 38%, respectively) [3]. Later, there were high expectations for a combination therapy of cisplatin with doxorubicin, hexamethylmelamine, cyclophosphamide and various other drugs. Until recently, the Gynecologic Oncology Group recommended a combination of cisplatin with cyclophosphamide as standard treatment [4]. This was supported by a meta-analysis which suggested that platinum combinations seem

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generally better than single-agent platinum when platinum is used at the same dose [5]. Despite the large amount of research, however, no general consensus has been reached on the comparative efficacy of a polychemotherapy containing platinum-based compounds and monochemotherapy with cisplatin or carboplatin [6]. In particular, the combination of cyclophosphamide with cisplatin has been the subject of debate, and a large-scale Italian multicentre trial comparing cisplatin single-agent with cisplatin combined either with cyclophosphamide alone (CP) or with cyclophosphamide and doxorubicin (CAP) failed to show a benefit for cyclophosphamide [7]. No significant difference was observed between the three study arms for progression-free and overall survival. Cyclophosphamide is, therefore, not considered to be an important addition to single-agent cisplatin. At the same time, we at the Norwegian Radiumhospital conducted a randomised phase III trial comparing cisplatin with CP. We are now able to report the 10-year survival rates of this study.

PATIENTS AND METHODS

Patients having biopsy-proved epithelial ovarian carcinoma with an International Federation of Gynecology and Obstetrics (FIGO) stage IIb–IV, residual lesions measuring more than 1 cm in diameter, a World Health Organisation performance status of 0–2, and adequate bone marrow and renal function were enrolled from January 1985 to February 1988 in the prospective randomised phase III trial at The Norwegian Radiumhospital: 181 patients were randomised, (Figure 1), 5 of whom were excluded (3 had borderline histology, 1 had a second primary tumour, and 1 had a residual tumour less than 1 cm). The extent of disease before treatment was determined by surgical exploration, with the intention to debulk the patient. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy were performed when feasible. All metastatic lesions were confirmed by histology or cytology. Primary surgery was performed in 44 and 132 patients at the Norwegian Radiumhospital and local hospitals, respectively, and induction chemotherapy was initiated in all patients at our department 2–4 weeks after surgery. All histological slides were reviewed at the Department of Pathology. Histological classification was based on criteria defined by the World Health Organisation [8]. Clear cell carcinomas were not graded.

The patients were randomly allocated to receive either cisplatin 75 mg/m^2 or cisplatin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (CP) every 28 days for six courses. In the case of a partial response (PR), treatment could be continued to a total of up to ten cycles of chemotherapy. The different dosages of cisplatin in the two arms were chosen to compare equitoxic regimens. Patient characteristics are shown in Table 1.

Conventional definitions of response were used according to the criteria of the World Health Organisation [9]. A complete response (CR) required the disappearance of all detectable tumours. A PR required a $\geq 50\%$ reduction in the cross-sectional area of the indicator lesions without growth or appearance of any other lesions. Either category of response required documentation by two observations at least 4 weeks

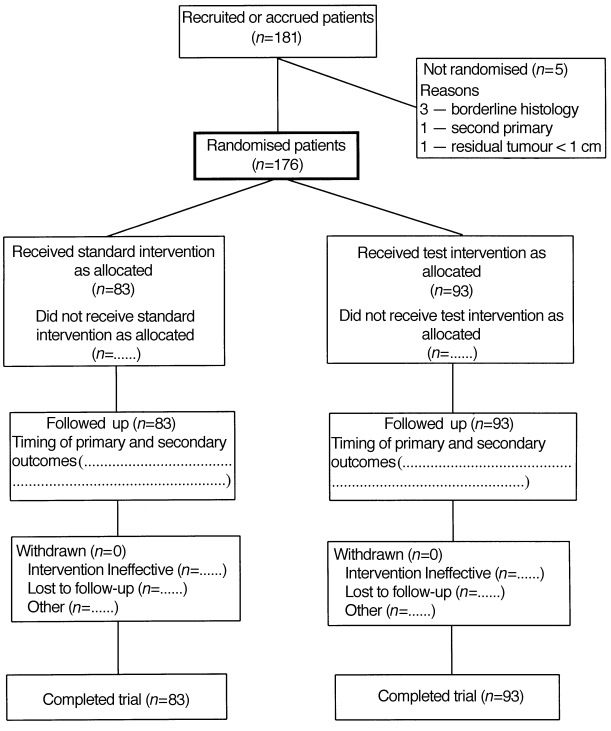

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood, S, *et al.* Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639).

Table 1. *Patient characteristics*

	Cisplatin	CP	*P* value
Number of patients	93	83	
Age			
Median	57	59	n.s.
Range	28–74	24–73	
Performance status			
0	39 (42%)	48 (58%)	n.s.
1	38 (41%)	21 (25%)	
2	16 (17%)	14 (17%)	
FIGO stage			
II	5 (5%)	2 (2%)	n.s.
III	77 (83%)	62 (75%)	
IV	11 (12%)	19 (23%)	
Histology			
Serous	71 (76%)	55 (66%)	n.s.
Mucinous	4 (4%)	3 (4%)	
Endometrioid	6 (6%)	11 (13%)	
Mixed	4 (4%)	2 (2%)	
Clear cell	2 (2%)	5 (6%)	
Unclassified	5 (5%)	6 (7%)	
Others	1 (1%)	1 (1%)	
Grade			
1	11 (12%)	6 (7%)	n.s.
2	22 (24%)	26 (31%)	
3	58 (62%)	46 (55%)	
Not graded	2 (2%)	5 (6%)	
Operative treatment			
Biopsy only	21 (23%)	21 (25%)	n.s.
Extensive debulking	72 (77%)	62 (75%)	
Ascites			
Yes	64 (69%)	60 (72%)	n.s.
No	29 (31%)	23 (28%)	
Residual disease (cm)			
< 2	13 (14%)	8 (10%)	n.s.
2–5	28 (30%)	27 (33%)	
> 5	52 (56%)	48 (58%)	

CP, cisplatin plus cyclophosphamide; n.s., non-significant.

apart. Progression consisted of a $\geq 25\%$ increase in the cross-sectional area of any lesion or the appearance of any new lesion. Stable disease (SD) was defined as a less than 25% increase or a less than 50% reduction in the cross-sectional area of any lesion without the appearance of any new lesions. Second-look laparotomy was performed in 68 patients 6 months after the start of chemotherapy. The same criteria for response were applied in these patients, whereby pathological (cytology and histology negative) and macroscopic (no visible lesion but positive cytology or histology) CRs were included.

In the analysis of second-line treatment, we employed the standard definition for platinum-sensitive and platinum-resistant disease in epithelial ovarian cancer according to Markman and colleagues [10]. Platinum-sensitive disease was defined as disease in a patient previously responsive to first-line therapy, whose tumour recurred > 6 months after cessation of treatment. Platinum-resistant disease included individuals who actually progressed while receiving platinum-based treatment, patients whose best response to treatment was stable disease or women who relapsed less than 6 months following completion of the platinum-based treatment.

Second-line treatment was administered to 131 patients, whereby 59 (45%) received platinum-based treatment, in 53 cases as carboplatin single-drug. 39 patients (30%) were treated with anthracyclines, ifosphamide, etoposide, thiotepa, 5-fluorouracil, or tamoxifen, whereas radiotherapy was used as second-line treatment in 33 patients (25%).

Patients were followed-up by routine gynaecological examinations at the Norwegian Radiumhospital or at local hospitals at intervals of 3 months during the first 2 years, 6 months during the third and fourth years and thereafter once yearly. All patients were followed until death or to January 1997. Follow-up information was collected from the medical records and from the Cancer Registry of Norway. The median observation period of surviving patients was 10 years, ranging from 9 to 11.8 years.

Statistics

Data were analysed using the data package SPSS for Windows (SPSS Inc., Chicago, Illinois, U.S.A.) run on a personal computer. Differences between the groups were evaluated by the χ^2 test. Survival was calculated from the day of diagnosis until death, regardless of the cause of death. Progression-free survival was calculated from the day of diagnosis to the time of progression or recurrence. All randomised patients who met inclusion criteria were evaluated according to the intention-to-treat principle. Survival and progression-free survival curves were calculated for each treatment group with Kaplan–Meier estimates and compared with the log-rank test. A P value < 0.05 was considered significant.

RESULTS

A total of 176 patients were eligible for this study. A median survival time of 20.7 months was observed, while the 5- and 10-year overall survival rates were 19 and 9%, respectively. 93 and 83 patients were treated with cisplatin and CP, respectively. There were no significant differences between the study groups with respect to important prognostic factors (Table 1). The proportion of patients in FIGO stage IV versus stages II and III was higher in the CP group but was only of borderline significance ($\chi^2 = 3.797$, $P = 0.051$). The median number of chemotherapy cycles was six (ranging from one to ten) in both groups (non-significant), whereby 83 and 88% of patients in the CP and cisplatin groups, respectively, underwent more than three cycles (non-significant).

The overall clinical response rates (CR + PR) were 52 and 63% for CP and cisplatin, respectively (Table 2; non-significant). Second-look laparotomy was performed in 68 patients and allowed documentation of response by histological examination. Including these data, we did not observe a statistically significant difference in response rates in either treatment group. Localisation of recurrence was similar in patients treated with cisplatin and CP.

The median progression-free survival was 10 and 11.9 months for CP and cisplatin, respectively. The log-rank test with $\chi^2 = 2.84$ and $P = 0.092$ did not allow rejection of the null hypothesis of equivalence of either treatment arm (Figure 2b). No significant difference was observed for overall survival with a median of 19.4 and 21.5 months for CP and cisplatin, respectively (log-rank test, $\chi^2 = 2.29$, $P = 0.1299$; (Figure 2b)). The 5- and 10-year overall survival rates were 16 and 7% for CP and 23 and 11% for cisplatin, respectively. Since FIGO stage IV patients might have been over-represented in the CP group, we re-analysed our data by stratifying patients for stage. For FIGO stage III patients, median survival was 20.7 and 28.1 months for CP and cisplatin, respectively ($\chi^2 = 1.61$, $P = 0.204$), and median progression-free survival was 10 and 12.1 months for CP and cisplatin, respectively ($\chi^2 = 1.84$, $P = 0.175$). In FIGO stage IV patients, median survival was 14.6 and 14.7 months for CP and cisplatin, respectively ($\chi^2 = 0.03$, $P = 0.858$), and median progression-free survival was 7.3 and 7.8 months for CP and cisplatin, respectively ($\chi^2 = 0.04$, $P = 0.844$). When analysis of treatment was adjusted by the major prognostic factors (residual tumour size, FIGO stage, grade, histotype and WHO score) in a Cox model, results similar to those for the univariate analysis were obtained. The estimated hazards ratio of CP versus cisplatin was 1.1 with a 95% confidence interval (CI) of 0.9–1.3, indicating no significant difference.

Table 2. Response of ovarian carcinoma patients to platinum-containing therapy

	Cisplatin	CP	*P* value
Response (clinical only)			
CR	26 (28%)	18 (22%)	n.s.
PR	33 (35%)	25 (30%)	
SD	16 (17%)	14 (17%)	
PD	13 (14%)	21 (25%)	
Not evaluable	5 (5%)	5 (6%)	
Response (pathological and clinical)			
pCR	7 (8%)	6 (7%)	n.s.
macroCR	3 (3%)	4 (5%)	
clinCR	15 (16%)	6 (7%)	
PR	36 (39%)	29 (35%)	
SD	15 (16%)	13 (16%)	
PD	14 (15%)	22 (27%)	
Not evaluable	3 (3%)	3 (4%)	
Second look	38	30	
Recurrence			
None	21 (23%)	9 (11%)	n.s.
Local	62 (67%)	60 (72%)	
Distant	10 (11%)	14 (17%)	

n.s., non-significant; CP, cisplatin plus cyclophosphamide; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

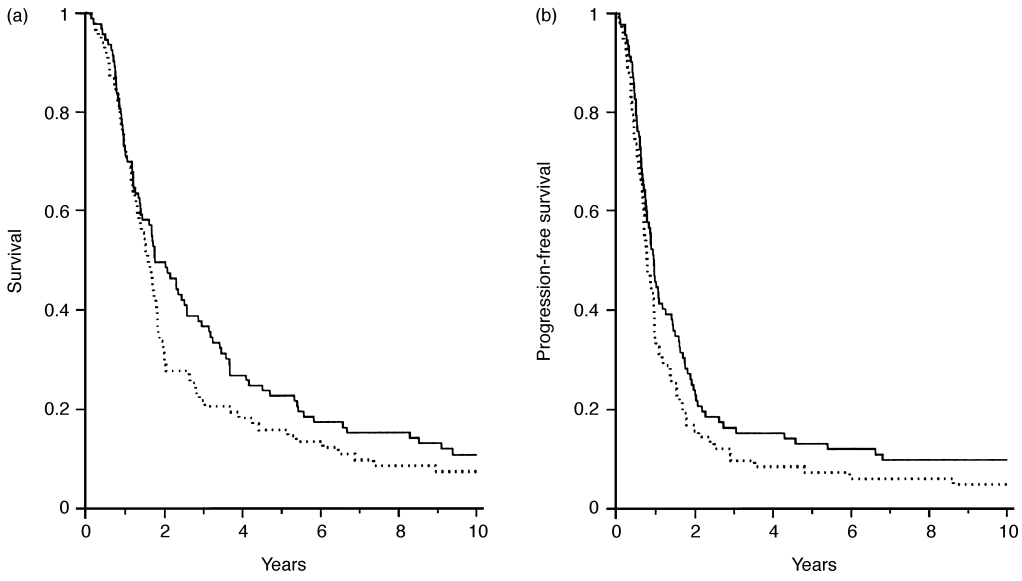

Figure 2. Overall survival (a) and progression-free survival (b) of ovarian cancer patients treated with either P (——) or CP (·····).

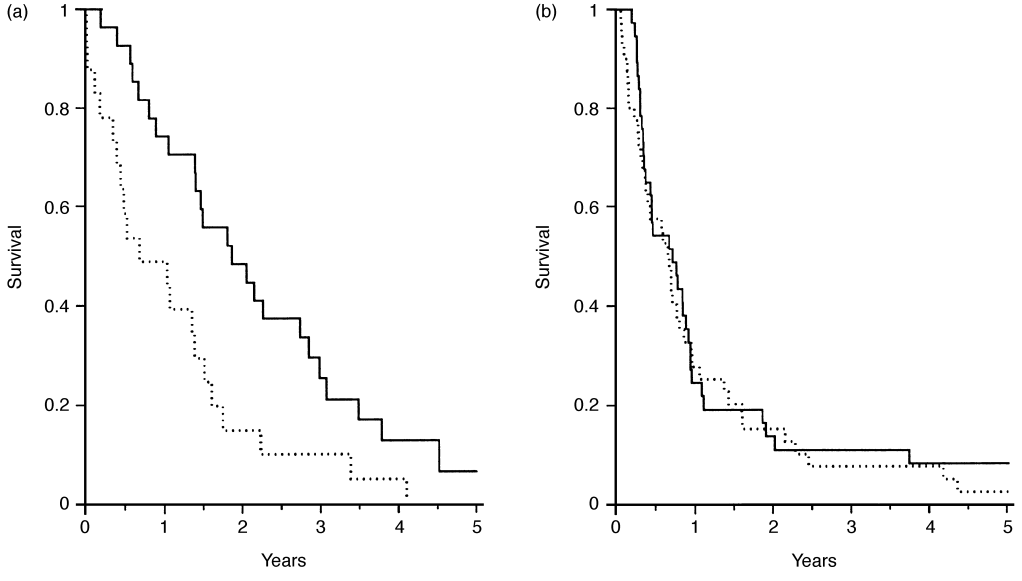

Figure 3. Survival curves of patients with platinum-sensitive tumours (a) and platinum-resistant tumours (b) treated with either platinum-containing (——) or platinum free (·····) therapy as second-line. Observation was calculated from initiation of second-line treatment.

Applying the criteria of Markman and colleagues [10], we observed platinum-sensitive tumours in 54 patients (58%) treated with cisplatin and in 59 patients (71%) treated with CP ($\chi^2 = 3.235$, $P = 0.072$). 37 platinum-resistant and 27 platinum-sensitive patients were treated with carboplatin or cisplatin as second-line therapy. Response rates to platinum second-line therapy were 6 and 50% for resistant and sensitive tumours, respectively (Table 3, $P < 0.001$). This difference in response rate was also confirmed by survival analysis. Patients with platinum-sensitive tumours survived longer when they were treated with platinum-containing chemotherapy (Figure 3a), $\chi^2 = 7.80$, $P = 0.005$). Median survival was 22.8 and 8.5 months after initiation of second-line treatment with platinum-containing and platinum-free regimens, respectively. In contrast, patients with platinum-resistant tumours showed no difference between the treatment groups (Figure 3b, $\chi^2 = 0.42$, $P = 0.519$). Median survival for these

Table 3. *Estimation of platinum sensitivity and response to platinum-containing second-line treatment*

	Resistant	Sensitive
Complete response	1 (3%)	5 (25%)
Partial response	1 (3%)	5 (25%)
Stable disease	10 (29%)	8 (40%)
Progressive disease	22 (65%)	2 (10%)
Not evaluable	3	7

Platinum-sensitive disease was defined as disease in a patient previously responsive to first-line therapy whose tumour recurred > 6 months after cessation of treatment. Patients not responding to primary therapy (stable or progressive disease) or with recurrence in ≤ 6 months were regarded as platinum-resistant. Results are presented as number of patients and in parentheses the percentage of patients evaluable for response. $\chi^2 = 19.93$, $P < 0.001$.

platinum-resistant patients was 8.8 and 8.1 months after initiation of second-line treatment for the platinum-containing and platinum-free regimens, respectively. However, the proportion of patients surviving 5 years after first recurrence ranged between 0 and 6% (non-significant) for the four groups (platinum-resistant and platinum-sensitive with and without platinum-containing second-line treatment).

DISCUSSION

This study does not indicate any significant difference in response, progression-free interval or overall survival between the two arms, CP versus cisplatin, even after 10 years of observation. This is in agreement with the large Italian randomised prospective study comparing cisplatin with CP with CAP [7]. Although the majority of patients in our trial had poor prognostic factors, e.g. residual disease > 2 cm in 88% of patients, the median survival time of 20.7 months was comparable to the 21.5 months observed in the similar study by CIGOC. Also, other small trials failed to observe a significant difference between single-agent cisplatin versus cisplatin combination [11–13]. A large meta-analysis suggested, however, that combination therapy is superior to platinum as a single agent [5]. Most of this difference may be attributed to the action of doxorubicin, since a large meta-analysis showed that CAP was superior to CP [14–16]. Our study, therefore, confirms that adding cyclophosphamide to cisplatin therapy may not significantly improve progression-free or overall survival. However, the dose for the CP regimen was substantially lower than the standard dose of CP (cisplatin 75 mg/m^2 and cyclophosphamide 750 mg/m^2 every 3 weeks). This suboptimal dose of CP might also be the explanation for the lower response rate, overall survival and progression-free survival in comparison with monotherapy with cisplatin. The question of whether or not cyclophosphamide adds benefit when given with an adequate dose of cisplatin would perhaps have been better answered by combining cisplatin at 75 mg/m^2 with 500 mg/m^2 cyclophosphamide. The possible role of anthracyclines is, however, not definitively clarified. Paclitaxel in combination with cisplatin has displaced cyclophosphamide as first-line treatment of ovarian cancer patients [17]. Whether anthracyclines as a third drug in combination with platinum plus a taxane further improves results is the subject of ongoing trials.

The interpretation of our results is complicated by the fact that dose and dose intensity of cisplatin differed in the two groups. Moreover, since the results concern a study initiated 10 years ago, the applied dose was below those generally used today. Most chemotherapeutic regimens considered as standard contain weekly cisplatin doses of at least 25 mg/m^2. In contrast, the planned weekly cisplatin dose intensity in our study ranged between 12.5 and 18.8 mg/m^2. The increase of 50% in dose intensity in a possibly suboptimal dose range did not significantly affect results. It is interesting to note that an increase in dose intensity of more adequate doses of cisplatin does not improve survival of ovarian cancer patients [18, 19]. However, although the 5- and 10-year survival rates in the cisplatin arm were 7 and 4% superior to those in the CP arm, this difference was not significant. This supports the concept that single-agent cisplatin is as good as combination therapy. This has recently been reinforced by the results from the Gynecologic Oncology Group study no. 132 [20]. 648 patients were randomised into a three-arm study comparing cisplatin (100 mg/m^2) with paclitaxel (200 mg/m^2 over 24 h) with the combination cisplatin plus paclitaxel (75 mg/m^2 and 135 mg/m^2 over 24 h, respectively). Observed response rates for cisplatin alone (74%) followed by paclitaxel were equivalent to cisplatin plus paclitaxel (72%). These and our findings suggest that sequential mono-chemotherapy is equally efficient in terms of overall and progression-free survival. However, toxicity with most combination regimens is greater than that for single-agent therapies. Sequential treatment with single agents may therefore improve life quality without reduction of patients' outcome.

One major interesting finding of our study was the outcome with second-line treatment. Patients with tumours considered platinum-sensitive according to the criteria of Markman and colleagues had a significantly higher response rate (50%) to platinum second-line treatment as compared with platinum-resistant tumours (6%). This is in agreement with several reports suggesting that patients with ovarian cancer who initially responded to cisplatin-based treatment and who subsequently developed recurrent disease can have a second response to retreatment with a cisplatin- or carboplatin-based regimen [21–24]. This difference in response was also confirmed by survival analysis. The median survival time was more than doubled in platinum-sensitive tumours subjected to platinum treatment. In contrast, patients with platinum-resistant tumours showed no significant effect of platinum treatment and their survival was similar to that for platinum-sensitive tumours treated with a non-platinum regimen. To our knowledge, this is the first demonstration of an effect of second-line platinum treatment on the survival of ovarian carcinoma patients. Platinum-based second-line treatment, however, could not achieve improved long-term survival, indicating a lack of efficacy as salvage therapy in these suboptimally operated ovarian carcinoma patients. It is very interesting that patients with cisplatin-resistant tumours had a similar survival unrelated to second-line therapy, and this was quite similar to that of patients with platinum-sensitive tumours treated with non-platinum-containing therapy (median survival was 8.8, 8.1, and 8.5 months, respectively). Platinum-containing second-line treatment is, therefore, a good possibility for platinum-sensitive tumours, whereas patients with platinum-resistant tumours should preferably be given a non-cross-reacting substance. The options applied in our study did not induce a sufficient response rate or survival.

1. Kristensen GB, Tropé C. Epithelial ovarian carcinoma. *Lancet* 1997, **349**, 113–117.
2. Tropé C. Melphalan with or without doxorubicin in advanced ovarian carcinoma. *Obstet Gynecol* 1987, **70**, 582–586.
3. Dørum A, Kristensen GB, Tropé C. A randomised study of cisplatin versus thiotepa as induction chemotherapy in advanced ovarian carcinoma. *Eur J Cancer* 1994, **30A**, 1470–1474.
4. Ozols RF, Young RC. Chemotherapy of ovarian cancer. *Semin Oncol* 1991, **18**, 222–232.
5. Advanced Ovarian Cancer Trialists Group. Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials. *Br Med J* 1991, **303**, 884–893.
6. NIH Consensus Development Panel on Ovarian Cancer. Ovarian Cancer. Screening, treatment, and follow-up. *J Am Med Assoc* 1995, **273**, 491–497.
7. GICOG (Gruppo Interregionale Cooperativo Oncologico Ginecologia). Long-term results of a randomized trial comparing cisplatin with cisplatin and cyclophosphamide with cisplatin, cyclophosphamide, and adriamycin in advanced ovarian cancer. *Gynecol Oncol* 1992, **45**, 115–117.

8. Serov SF, Scully RE, Sobin LH. Histological typing of ovarian tumors. *International Histological Classification of Tumors*, No. 9. Geneva, World Health Organization, 1973, 17–18.
9. Miller AB, Hoostrafien B, Staquet M, Winkler A. Reporting results in cancer treatment. *Cancer* 1981, **47**, 207–214.
10. Markman M, Rothman R, Hakes T, *et al.* Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991, **9**, 389–393.
11. Cohen CJ, Goldberg JD, Holland JF, *et al.* Improved therapy with cisplatin regimens for patients with ovarian carcinoma (FIGO Stages III and IV) as measured by surgical end-staging (second-look operation). *Am J Obstet Gynecol* 1983, **145**, 955–967.
12. Wiltshaw E, Evans B, Rustin G, Gilbey E, Baker J, Barker G. A prospective randomized trial comparing high-dose cisplatin with low-dose cisplatin and chlorambucil in advanced ovarian carcinoma. *J Clin Oncol* 1986, **4**, 722–729.
13. Tomirotti M, Perrone S, Gie P, *et al.* Cisplatin (P) versus cyclophosphamide, adriamycin and cisplatin (CAP) for stage III–IV epithelial ovarian carcinoma: a prospective randomized trial. *Tumori* 1988, **74**, 573–577.
14. Ovarian Cancer Meta-Analysis Project. Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin, and cisplatin chemotherapy of ovarian carcinoma: a meta-analysis. *J Clin Oncol* 1991, **9**, 1668–1674.
15. A'Hern RP, Gore ME. Impact of doxorubicin on survival in advanced ovarian cancer. *J Clin Oncol* 1995, **13**, 726–732.
16. Tropé C, Andersson H, Bjørkholm E, *et al.* Doxorubicin-melphalan with and without cisplatin in advanced ovarian cancer. Ten year survival results from a prospective randomized study by the Swedish Co-operative Ovarian Cancer Study Group. *Acta Oncol* 1996, **35**(Suppl. 8), 109–118.
17. 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.
18. McGuire WP, Hoskins WJ, Brady MF, *et al.* Assessment of dose-intensity therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 1995, **13**, 1589–1599.
19. Bolis G, Favalli G, Danese S, *et al.* Weekly cisplatin given for 2 months versus cisplatin plus cyclophosphamide given for 5 months after cytoreductive surgery for advanced ovarian cancer. *J Clin Oncol* 1997, **15**, 1938–1944.
20. Muggia FM, Braly PS, Brady MF, *et al.* Phase III of cisplatin (P) or paclitaxel (T), versus their combination in suboptimal stage III and IV epithelial ovarian cancer (EOC): Gynecologic Oncology Group (GOG) study #132. *Proc Am Soc Clin Oncol* 1997, **16**, 352a.
21. Thigpen JT, Vance RB, Khansur T. Second-line chemotherapy for recurrent carcinoma of the ovary. *Cancer* 1993, **71**(4 Suppl.), 1559–1564.
22. Gore ME, Fryatt I, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. *Gynecol Oncol* 1990, **36**, 207–211.
23. Hoskins PJ, O'Reilly SE, Swenerton KD. The 'failure free interval' defines the likelihood of resistance to carboplatin in patients with advanced epithelial ovarian cancer previously treated with cisplatin: relevance to therapy and new drug testing. *Int J Gynecol Cancer* 1991, **1**, 205–208.
24. Gershenson DM, Kavanagh JJ, Copeland LJ, Stringer CA, Morris M, Wharton JT. Retreatment of patients with recurrent epithelial ovarian cancer with cisplatin-based chemotherapy. *Obstet Gynecol* 1989, **73**, 798–802.