Eur J Cancer Clin Oncol, Vol. 22, No. 11, pp. 1271–1277, 1986.
Printed in Great Britain

0277-5379/86$3.00+0.00

Special Article

European Studies with Cisplatin and Cisplatin Analogs in Advanced Ovarian Cancer

C. SESSA*

Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

INTRODUCTION

In about 80% of women with epithelial ovarian cancer the tumor is already extended within the abdomen at the time of diagnosis. From the early fifties, chemotherapy with alkylating agents represented the treatment of choice for FIGO stage III–IV, inducing a clinical tumor response in 40–50% of patients, and a clinical complete remission in 10% of them [1]. However, the impact of chemotherapy on 5-yr survival was minimal.

In 1974, cisplatin was reported to produce tumor regression in patients resistant to alkylating agents [2]. These promising results were widely confirmed in subsequent studies, and today cisplatin is the drug of choice in advanced ovarian cancer. Nevertheless, more than 10 yr after its initial appearance, it remains unclear, at least with respect to this neoplasia, how we can take full advantage of its antitumor activity and of the reduced toxicity of its analogs.

Answers to these intriguing questions could perhaps be provided by a critical review of different aspects of the most significant ovarian cancer trials performed in Europe with platinum compounds.

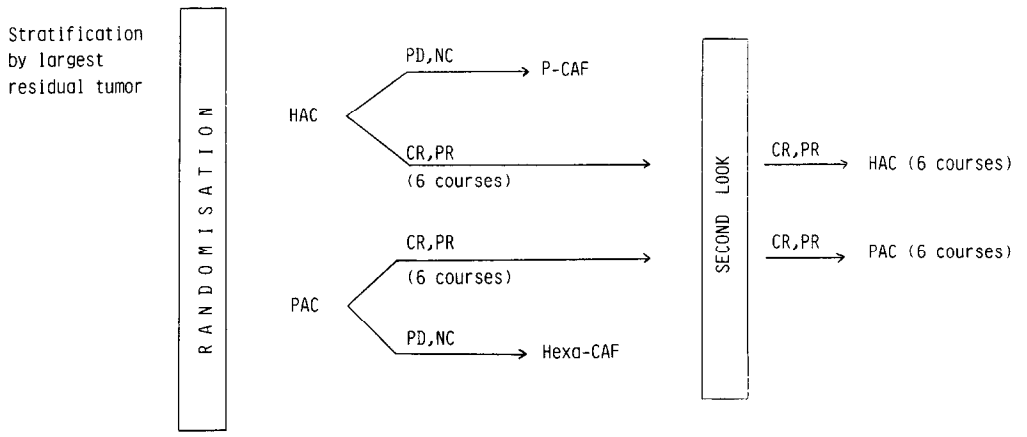
EUROPEAN STUDIES WITH CISPLATIN

In 1978 Young published the results of a randomised study of Hexa-CAF vs. L-PAM [3]: the four-drug regimen appeared to be more effective than melphalan, inducing twice as many surgical complete responses (33% vs. 16%), and a more prolonged median survival time (29 vs. 17 months). At the same time, Eve Wiltshaw at the Royal Marsden Hospital was treating patients resistant to alkylating agents with an experimental drug, cisplatin [2, 4, 5]. The progressive increase of the response rate from 26 to 52%, which paralleled the progressive increase of the dose from 30 to 100 mg/m^2, and above all the appearance of complete remissions in this unfavourable population, suggested that cisplatin was really one new active drug. Already well known were the data of Griffith showing a strict relationship between survival and size of largest residual disease [6]. Patients with a residual tumor of more than 1.5 cm after primary surgery had a worse survival rate than patients who had a residual tumor size below this limit at diagnosis or after excision of larger metastases.

All these data (i.e., showing that the Hexa combination was more effective than single alkylating agents, that cisplatin produced a greater than 30% response in patients resistant to alkylating agents, that the size of largest residual disease before chemotherapy was an independent predictor for survival), together with the clinical experience that second-look surgery was essential for a better definition of response and treatment duration represented biologic rationales of the first trial with cisplatin combination chemotherapy which we started in 1978 in Milan together with Costantino Mangioni (Fig. 1). Patients, stratified by largest size of residual disease, were randomly allocated to receive adriamycin (ADM) and cyclophosphamide (CTX) in combination with hexamethylmelamine (HMM) (HAC) or cisplatin (PAC) administered at 50 mg/m^2. Patients in response or with no clinically evaluable disease were submitted to second look surgery after six courses.

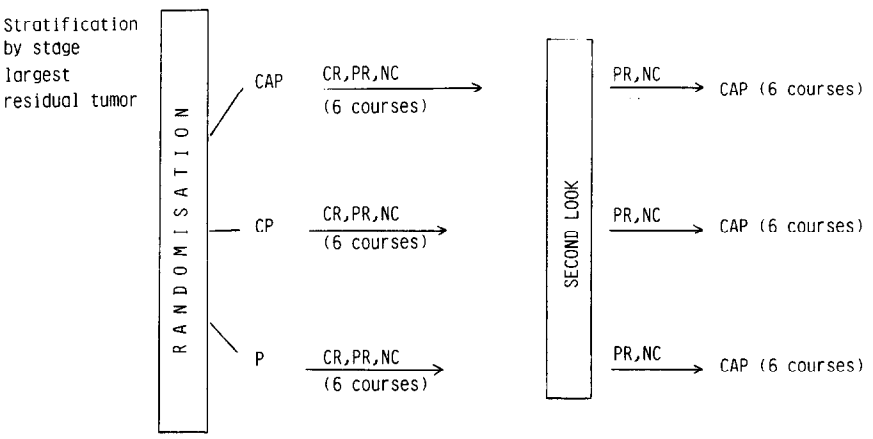
The interim analysis of this study, performed in October 1980 on 102 evaluable patients, showed

Accepted 25 April 1986.
*Lecture given at the ECCO-3 in Stockholm (June 1985) as a recipient of the first award of the European Society for Medical Oncology (ESMO) for a young European medical oncologist with distinct merits in cancer research.
Reprint requests: C. Sessa, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland.



H = Hexamethylmelamine 150 mg/sqm p.o. D 1-14 every 4 weeks
A = Adriamycin 50 mg/sqm i.v. D 1 every 4 weeks
C = Cyclophosphamide 70 mg/sqm p.o. D 1-14 every 4 weeks
P = Cisplatin 50 mg/sqm i.v. D 1 every 4 weeks

Fig. 1. First trial with cisplatin combination chemotherapy in Stage III-IV ovarian cancer, study design.



C = Cyclophosphamide 600 mg/sqm i.v. D 1 every 4 weeks
A = Adriamycin 50 mg/sqm i.v. D 1 every 4 weeks
P = Cisplatin 50 mg/sqm i.v. D 1 every 4 weeks

Fig. 2. Second trial with cisplatin combination chemotherapy in Stage III-IV ovarian cancer, study design.

a similar overall clinical response rate of 78% to both treatments [7]. However, in patients with more than a 2 cm residual disease, the surgical complete response rate was 38% after PAC and 11% after HAC ($P < 0.025$) with, respectively, 46 and 9% of the patients free of disease at 1 yr ($P < 0.01$). We concluded that PAC was more effective than HAC in inducing surgical complete responses and that the induction of surgical complete response was the most important determinant of disease free survival. Hence, the study was closed to patient accrual.

At that time, the beginning of 1981, on the basis of the available data Hexa combinations still appeared to be more effective than single alkylating agents, but cisplatin combinations seemed to be even more effective than Hexa combinations, as suggested by the interim analysis of our first trial and of the three-arm study of the Princess Margaret Hospital [8]. Furthermore, as reported by Erlich who also tested the PAC regimen, low-dose (50 mg/m^2) cisplatin combinations seemed to be as effective as high-dose (100 mg/m^2) combinations, with both regimens producing a quite severe hematological toxicity [9]. It was clear that cisplatin was becoming the drug of choice in ovarian cancer but we could not define its particular activity in untreated patients as it had been used only in combination. Must cisplatin always be used in combination or could it be used alone, thus reducing toxicity? In other words, as PAC seemed to be the most effective treatment available, what was the contribution in activity of the alkylating agents and/or adriamycin? The specific aim of the second trial with a cisplatin combination chemotherapy, started in 1981 in Milan, was therefore to compare the efficacy and toxicity of three different regimens with cisplatin at 50 mg/

Table 1. *Second trial with cisplatin combination chemotherapy in stage III-IV ovarian cancer. Interim results* (1985)

Treatment	No. of evaluable patients	SR* (%)	CR (%)	PR (%)	NR (%)	Median survival (months)	% surviving at 2 yr
CAP	136	87 (64)	30 (22)	57 (42)	49 (36)	27.5	56
CP	128	76 (60)	28 (22)	48 (38)	52 (40)	19.3	46
P	128	67 (52)	17 (13)	50 (39)	61 (43)	20	43

*Surgical responders.

m^2 (Fig. 2). In the first arm cisplatin was given as part of the CAP regimen which had been tested in the previous study. ADM was eliminated from the second arm (CP), while in the third arm (P) cisplatin was given alone. Second-look surgery was performed in responding patients after six courses. Partial responders with macroscopic residual disease not suitable for radiation therapy continued with CAP in all three arms for six further courses or until progression of disease.

While the first trial was carried out only in one institution, the second was carried out in six different ones in northern Italy, all of them members of an inter-regional gynaecologic oncology cooperative group. Table 1 shows the results of the interim analysis performed in May 1985. The overall surgical response rate was 64% to CAP, 60% to CP and 52% to P. Surgical complete remission was achieved in 22% of the patients treated with CAP and CP, and in 13% of the patients treated with cisplatin alone. Median overall survival was 27.5 months after CAP, 19.3 after CP, and 20 months after P. Fifty-six per cent, forty-six per cent and forty-three per cent of the patients treated with CAP, CP and P, respectively, were alive at 2 yr. On the basis of these preliminary results cisplatin in combination appeared to be more effective than cisplatin alone in terms of surgical response, even though a longer follow-up would be required to establish whether this higher complete remission rate would result in a higher percentage of long-term survivors. On the other hand, it was already clear that CAP produced significantly more hematologic toxicity and alopecia than CP or P.

Meanwhile, when at the end of 1983 we again analysed the data of the first trial, we found that in patients with more than a 2 cm residual disease the surgical complete response rates to HAC (13%) and PAC (21%) were no longer significantly different and that the complete response rates were also identical in patients with less than a 2 cm residual disease [10]. The overall median survival time was similar after HAC and PAC (23 and 24 months, respectively). We had therefore to conclude that at a median follow-up time of 36 months, PAC was as effective as HAC in terms of response, duration of remission and survival. However, given the small number of patients entered because of the premature interruption of the study, the power of the statistical test was such as to allow only the detection of differences in complete response rate equal to or more than 80%. Differences in response or survival of a lesser order of magnitude might have been missed.

The results achieved with cisplatin alone have convinced us that this drug is definitely the one of choice in advanced ovarian cancer. However, as the manner in which cisplatin should be applied in this disease is still a matter of debate, what could be expected from increasing the dose, or, in other words, what would have happened if we had used cisplatin at 100 or 120 mg/m^2 instead of 50 mg/m^2? The efficacy and toxicity of high-dose cisplatin have primarily been evaluated in combination. In a randomised study Neijt compared a combination of cisplatin (20 mg/m^2 on days 1 to 5), ADM, CTX and HMM (CHAP-5) with a combination without it (the Hexa-CAF regimen) [11]. The overall and complete surgical response rates to CHAP-5 were, respectively, 79 and 39%, significantly higher than those obtained in the Hexa-CAF groups (50 and 19% respectively). Time to progression and overall survival were also significantly higher after CHAP-5 than after Hexa-CAF. Apart from the hematologic toxicity, which was more severe with the cisplatin combination (with leucopenia and grade 3–4 thrombocytopenia occurring in 61 and 30% of patients after CHAP-5 and in 40 and 10% of patients after Hexa-CAF), the incidence of side-effects ascribable only to cisplatin was high. Mild to severe peripheral neuropathy occurred in more than 50% of patients while 59% showed cumulative mild renal dysfunction.

This study showed that a high-dose cisplatin

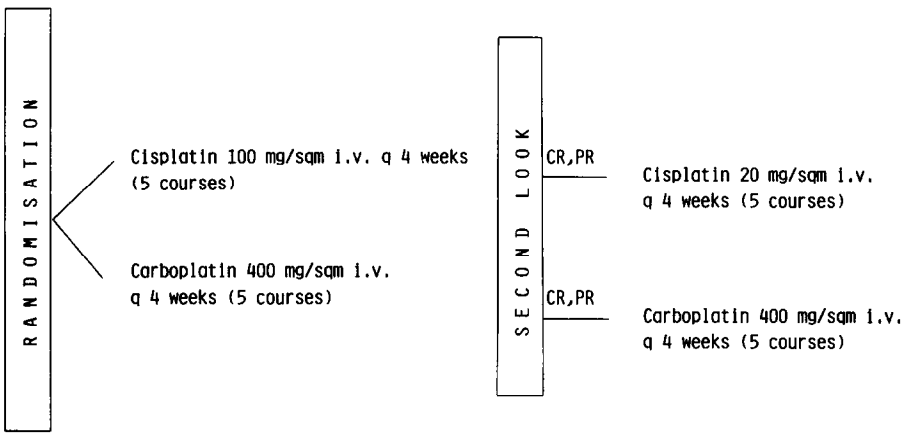


Fig. 3. Cisplatin versus carboplatin in Stage III-IV ovarian cancer, study design.

combination resulted in approx. 30% of surgical complete remissions; however, the regimen was very toxic and produced a survival advantage only in the group of patients with small residual disease. It is therefore important to establish definitely whether high-dose cisplatin combinations are more effective than low-dose ones. However, no randomised clinical studies have been planned to test high-dose cisplatin, alone or in combination, versus low-dose cisplatin, alone or in combination. Furthermore, there are no randomised data on the use of high-dose cisplatin alone vs. high-dose cisplatin in combination.

EUROPEAN STUDIES WITH CISPLATIN ANALOGS

The efficacy and toxicity of high-dose cisplatin-alone were evaluated in a randomised study begun in 1981 at the Royal Marsden Hospital comparing single-dose cisplatin (100 mg/m^2) and carboplatin (400 mg/m^2) as first-line treatment.

As one of several cisplatin analogs, carboplatin was selected for clinical investigation on the bases of reduced nephrotoxicity in rats, and increased antitumor selectivity in many tumor test systems. The significant activity in ovarian cancer reported in the phase I study [12], was confirmed in the subsequent phase II study performed at the Royal Marsden Hospital, with more than 20% of objective remissions in patients pretreated with cisplatin [13].

Figure 3 shows the design of the cisplatin versus carboplatin study. Surgical evaluation of response was performed after five courses in responders or in patients with no clinically evaluable disease. Surgical responders received five additional courses. Patients with progressive disease after two cycles, or stable disease after four, or with severe toxicity were crossed over to the other arm of the study.

A preliminary analysis performed on 112 evaluable patients showed a similar, surgically-documented, response rate of 64% to cisplatin and 57% to carboplatin with a 24% surgical complete response rate in both treatments [14]. Cisplatin administration was stopped in 47% of patients because of severe non-hematological toxicity. The incidence of non-hematological toxicity was analysed according to the sequence of treatment. Peripheral neuropathy was reported in 35% of the patients receiving cisplatin as first treatment, while it developed in none of the patients on carboplatin. Ten per cent of the patients receiving cisplatin after carboplatin had neurological disturbances, while peripheral neuropathy occurred in 24% of the patients receiving carboplatin after previous therapy with cisplatin. Renal toxicity, defined as more than a 40% fall in EDTA clearance after three courses, occurred in 49% of patients with first treatment cisplatin but only in 5% of the patients receiving first-treatment carboplatin. No renal toxicity was reported in 23 patients receiving second-treatment carboplatin. As expected, thrombocytopenia was more common after carboplatin than after cisplatin.

On the basis of these results, it appears that while the two show similar activity, carboplatin is associated with a lesser degree of non-hematological toxicity than is high-dose cisplatin. Longer follow-up and additional data are obviously required to establish whether carboplatin can replace high-dose cisplatin. However, in view of the observed striking difference between the non-hematological toxicities of these two drugs, and also considering the increased neurotoxicity and hematological toxicity of carboplatin after previous treatment with cisplatin, it would seem difficult to repeat this study, or at any rate with the same cisplatin schedule.

How might the similar promising data on other

cisplatin analogs which are becoming available be utilized to improve survival and, above all, the quality of the lives of patients with advanced ovarian cancer?

We know that only surgical complete remissions will translate into prolonged survival and that some biologic characteristics of the tumor, such as size of largest residual disease before chemotherapy, stage at presentation (III or IV), histological grade and perhaps histological type, are independent predictors for complete remission. With these premises, how might we attempt to increase the response rate with an acceptable level of toxicity and to maintain the complete remissions achieved? The latter question is also very important because of the fact that about 30% of surgical complete responders still suffer a tumor relapse. The value of radiotherapy and intraperitoneal therapy in this context is being tested in many ongoing studies, and their results are awaited with interest.

The overall response rate could be significantly improved by increasing the number of complete responses to first treatment, a goal which probably could be achieved only in patients with small residual disease. Possible strategies could be the use of cisplatin analogs in combination, in view of their reduced non-hematological toxicity and of the possibility of a more feasible control of the hematological toxicity; concomitant or alternating i.v. administration of cisplatin and cisplatin analogs, singly or in combination; concomitant use of cisplatin and cisplatin analogs with different schedules and ways of administration.

The overall response rate could also be significantly increased by improving the number of complete responses achieved by second treatment, a goal which probably could be reached only in patients still responding to first-line chemotherapy. In fact, the majority of these patients have an unresectable diffuse macroscopic residual disease not suitable for local therapy. Possible strategies could be represented by treatments with the same drugs at higher dosages, or by treatments with known active drugs not as yet administered. Cisplatin analogs can play a role in this context, as shown by the preliminary results of the cross-over applied in the study of cisplatin versus carboplatin (Table 2). Four partial responders to carboplatin were reported out of 21 patients pretreated with cisplatin, and three out of 15 patients who did not respond to cisplatin (Table 2A). The fourth response occurred in the only patient who stopped therapy while in response and relapsed 8 months after the last cisplatin administration. Out of 21 patients pretreated with carboplatin, four responded to second treatment cisplatin (Table 2B). Three responses were observed out of the 17 patients primarily resistant to carboplatin, while the fourth response again occurred in the only patient who relapsed off treatment.

Antitumor activity in ovarian cancer was also reported in the phase I study of another non-nephrotoxic analog, iproplatin [15]. For this reason, the Early Clinical Trials Group decided in 1984 to start a disease-oriented phase II study in previously treated/untreated ovarian cancer patients. Table 3 reports the preliminary results achieved among 84 patients previously treated with cisplatin [16]. All but one of the 15 responses achieved were observed in the 29 patients who stopped cisplatin while still responding, while only one response occurred out of 12 patients who relapsed during treatment. None of the 37 patients primarily resistant to cisplatin responded to iproplatin.

As suggested by the previous results, second-

Table 2. Cisplatin vs. carboplatin in stage III–IV ovarian cancer. Results of the cross-over study

2A. Response to carboplatin in patients previously treated with cisplatin

Cisplatin stopped for	No. of patients	CR	PR	NR	NE
End of treatment	1	0	1	0	0
No response	15	0	3	11	1
Relapse	5	0	0	5	0

2B. Response to cisplatin in patients previously treated with carboplatin

Carboplatin stopped for	No. of patients	CR	PR	NR	NE
End of treatment	1	0	1	0	0
No response	17	1	2	12	2
Relapse	3	0	0	3	0

Table 3. Phase II study of iproplatin in advanced ovarian cancer. Response in patients previously treated with cisplatin

Cisplatin stopped for	No. of patients	Response CR	PR	NC	PD	TE	NE
End of treatment	29	3	11	4	7	1	3
Toxicity	6	0	0	2	2	1	1
Relapse	12	0	1	1	5	4	1
No response	37	0	0	3	22	6	6

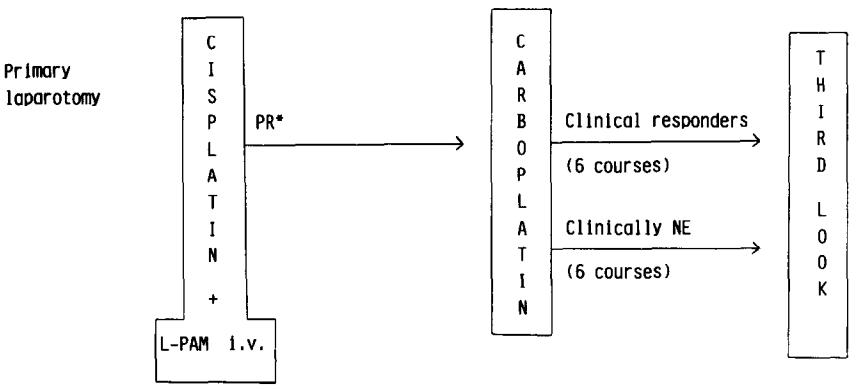


Fig. 4. Phase II study of carboplatin in advanced ovarian cancer patients pretreated with cisplatin, study design.

line treatment with analogs could be effective in patients still responding or in those not clearly resistant to cisplatin, while their activity in patients definitely resistant to cisplatin should be further defined, at least that of carboplatin. Therefore, one way of inducing complete remission in partial responders could be the use of carboplatin after first-treatment cisplatin, as in the Swiss ongoing phase II study (Fig. 4). Carboplatin is administered to patients who achieved a surgically-verified partial response with macroscopic residual disease after four to six courses of cisplatin in combination with L-PAM IV as first-line therapy. Clinical responders or patients with no clinically evaluable disease are submitted to a third-look laparotomy after six courses of carboplatin.

Finally, we can try to improve the response rate in patients with stage IV or bulky stage III. In fact, the survival of these patients has not been prolonged by current therapies, with more than 80% of patients dying within 2 yr from diagnosis. We need new active drugs in ovarian cancer but, as in other malignancies for which there exist partially effective treatments, we can fail to detect the potential activity of new agents when testing them in a heavily pretreated population [17] or in one merely resistant to cisplatin [18]. We should therefore consider the possibility of testing selected experimental drugs as first treatment in those ovarian cancer patients who are unlikely to benefit from standard therapies because of the unfavourable characteristics of their disease.

CONCLUSION

As 70–80% of patients with advanced ovarian cancer have large residual disease, the so-called favourable group of patients is quite small. More knowledge and more accurate evaluation of the biologic characteristics of this tumor could improve treatment results at least in this selected population. However, it must be borne in mind that greater knowledge and reliable results can be achieved only through simply designed, large cooperative controlled studies asking a restricted number of selected relevant questions.

Acknowledgements—The author wishes to acknowledge the help of the coordinators of the studies reported in this review as well as that of her other friends with whom she has had the opportunity of working: C. Mangioni, S. Marsoni, H. Calvert, E. Wiltshaw, F. Cavalli and A. Goldhirsch.

REFERENCES

1. Tobias JS, Griffiths CT. Management of ovarian carcinoma. Current concepts and future prospects. *N Engl J Med* 1976, **294,** 818–823, 877–882.
2. Wiltshaw E, Kroner T. Phase II study of *cis*-dichlorodiammineplatinum (II) (NSC-119875) in advanced adenocarcinoma of the ovary. *Cancer Treat Rep* 1976, **60,** 55–60.
3. Young RC, Chabner BA, Hubbard SP *et al.* Advanced ovarian carcinoma. A prospective clinical trial of melphalan (L-PAM) versus combination chemotherapy. *N Engl J Med* 1978, **299,** 1261–1266.
4. Wiltshaw E. A review of clinical experience with *cis*-platinum diammine dichloride: 1972–1978. *Biochimie* 1978, **60,** 925–929.
5. Wiltshaw E. Subramarian S, Alexopoulos C, Barker GH. Cancer of the ovary: a summary of experience with *cis*-dichlorodiammineplatinum (II) at the Royal Marsden Hospital. *Cancer Treat Rep* 1979, **63,** 1545–1548.
6. Griffiths CT, Parker LM, Fuller AF. Role of cytoreductive surgical treatment in the management of advanced ovarian cancer. *Cancer Treat Rep* 1979, **63,** 235–240.
7. Mangioni C, Bolis G, Valente I *et al. Cis*-diamminedichloroplatinum, adriamycin, cyclophosphamide (PAC) vs. hexamethylmelamine, adriamycin and cyclophosphamide (HAC) in advanced ovarian cancer. *Proc Am Assoc Cancer Res* 1981, **166.**
8. Sturgeon JFG, Fine S, Gospodarowicz MK *et al.* A randomized trial of melphalan alone versus combination chemotherapy in advanced ovarian cancer. *Proc Am Assoc Cancer Res and ASCO* 1982, **108.**
9. Ehrlich CE, Einhorn L, Williams SD, Morgan J. Chemotherapy for stage II-IV epithelial ovarian cancer with *cis*-dichlorodiammineplatinum (II), adriamycin, and cyclophosphamide: a preliminary report. *Cancer Treat Rep* 1979, **63,** 281–288.
10. Sessa C, Bolis G, Colombo N *et al.* Hexamethylmelamine, adriamycin and cyclophosphamide (HAC) versus *cis*-dichlorodiammineplatinum, adriamycin and cyclophosphamide (PAC) in advanced ovarian cancer: a randomized clinical trial. *Cancer Chemother Pharmacol* 1985, **14,** 222–228.
11. Neijt JP, Van Der Burg MEL, Vriesendorp R *et al.* Randomised trial comparing two combination chemotherapy regimens (Hexa-CAF vs. CHAP-5) in advanced ovarian carcinoma. *Lancet* 1984, 594–599.
12. Calvert AH, Harland SJ, Newell DR *et al.* Early clinical studies with cis-diammine-1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol* 1982, **9,** 140–147.
13. Evans BD, Raju KS, Calvert AH *et al.* Phase II study of JM8, a new platinum analog, in advanced ovarian carcinoma. *Cancer Treat Rep* 1983, **67,** 997–1000.
14. Wiltshaw E, Evans B, Harland S. Phase III randomised trial cisplatin versus JM8 (carboplatin) in 112 ovarian cancer patients, stages III and IV. *Proc Am Assoc Cancer Res and ASCO* 1985, **121.**
15. Bramwell VHC, Crowther D, O'Malley S *et al.* Activity of JM9 in advanced ovarian cancer: a phase I-II trial. *Cancer Treat Rep* 1985, **69,** 409–416.
16. Sessa C, Cavalli F, Kaye S *et al.* Phase II study of cis-dichloro-trans-dihydroxy-bis-isopropylamine platinum IV (CHIP) in advanced ovarian carcinoma. *Proc Am Assoc Cancer Res and ASCO* 1985, **116.**
17. Wittes RE, Marsoni S, Simon R, Leyland-Jones B. The phase II trial. *Cancer Treat Rep* 1985, **69,** 1235–1239.
18. Sessa C, D'Incalci M, Colombo N *et al.* Lack of activity of cyclophosphamide in ovarian cancer patients refractory to *cis*-dichlorodiammine platinum. *Cancer Chemother Pharmacol* 1983, **11,** 33–34.