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Current status of systemic chemotherapy in the treatment of advanced ovarian cancer with emphasis on CHAP-5

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Summary

In patients with advanced ovarian cancer, initial treatment with combination chemotherapy, including cyclophosphamide and *cis*-platinum diamminedichloride (*cis*-platinum), produces response and progression-free survival results which are superior to those achieved with alkylating single-agent chemotherapy. Unfortunately most schedules have not resulted in a statistically significant improvement of overall survival. So far one of the most effective combination regimens is the four-drug regimen CHAP-5 that consists of cyclophosphamide, hexamethylmelamine, adriamycin, and *cis*-platinum. This regimen is the first schedule to result in significant improved survival times compared with a second combination schedule, i.e. Hexa-CAF, which is at least as good as alkylating therapy alone. The CHAP-5 regimen was rather toxic but it was manageable and easy to apply in daily practice. Further improvement of the treatment results in advanced ovarian carcinoma will be difficult because no effective new drugs are available. In future clinical research it must be tried to decrease the toxicity and morbidity of the current schedules without reducing efficacy and survival.

Introduction

Many interesting studies have been initiated in the last decade to answer a number of questions about the treatment of epithelial ovarian cancer. The results of the most recent studies have not been published definitely but preliminary analysis indicates that progress has been made and that we are now able to offer better perspectives to our patients. In this paper emphasis will be on the improvement of the results with cytotoxic treatment in advanced disease. Although radiotherapy might have a place in the treatment of ovarian cancer when there is minimal residual disease, it is yet to be established whether radiotherapy, chemotherapy or a combined modality approach is the treatment of choice. Most of the relevant studies have not led to definite conclusions because pretreatment staging was in-

adequate, the irradiation field or dosage was not sufficient, or the chemotherapy delivered was not optimal [13,24,58]. In patients with bulky disease as in patients with a FIGO stage IV (distant metastases to the liver or any other site in the body outside the abdominal cavity) radiotherapy has been used without success [19]. In these patients systemic chemotherapy is definitely the treatment of choice.

Single-agent chemotherapy

It has been shown that alkylating agents are useful in the treatment of ovarian cancer. The response rates mentioned for alkylating agents in the literature range from 11% [10] to 67% [16]. This variation is due to different risk factors in patient populations and different response criteria. Table I shows the cumulative results in 2037 patients treated with alkylating chemotherapy. The total response rate amounts to 42% and the median survival time is approximately 14 months. In patients who achieve a remission survival is prolonged, but only a small percentage will reach long-term survival. The overall 5-year survival rate is less than 10% [27,46,63]; none of the non-responders will survive and only 16% of those who responded to chemotherapy. The observation that responding patients may survive for more than 5 years has encouraged clinical research to identify more powerful chemotherapy regimens which may improve the number of long-term survivors and even cure patients of their advanced disease.

Clinical trials provided results showing that none of the available alkylating agents was superior to any other. Although the questions of high versus low dose, intermittent versus daily drug dose scheduling, oral versus intravenous administration, and drug dose loading have not been thoroughly stud-

TABLE I

Treatment results obtained with alkylating agents as initial chemotherapy in patients with advanced ovarian carcinoma[a].

Agent	No. of patients evaluable	No. of clinical responses	Median survival (mths)	Reference
Melphalan	72	29 (40)	11	50
Melphalan	16	4 (25)	20	23
Melphalan	38	18 (47)	20	48
Melphalan	72	29 (40)	19	53
Melphalan	61	18 (30)	12	39
Melphalan	70	8 (11)	–	10
Melphalan	37	20 (54)	17	60
Melphalan	64	24 (38)	–	34
Melphalan	114	30 (26)	28	9
Melphalan	23	7 (30)	14	51
Melphalan	541	252 (47)	–	49
Cyclophosphamide	27	18 (67)	–	16
Cyclophosphamide	29	18 (62)	11	15
Cyclophosphamide	115	25 (21)	11	42
Cyclophosphamide	35	11 (31)	12	17
Cyclophosphamide	335	144 (43)	–	49
Chlorambucil	388	196 (50)	–	49
Total	2037	851 (42)	14[b]	

[a] Figures in parentheses are percentages.
[b] Median value.

TABLE II

Treatment results obtained with non-alkylating agents as initial chemotherapy in patients with advanced ovarian carcinoma[a].

Agent	No. of patients evaluable	No. of clinical responses	Median survival (mths)	Reference
cis-Platinum	9	6 (67)	-	22
cis-Platinum	22	11 (50)	21	20
cis-Platinum	13	4 (13)	20	11
Hexamethylmelamine	54	17 (32)	15	55
Adriamycin	12	6 (50)	-	36
Adriamycin	12	4 (33)	-	47
Adriamycin	19	8 (42)	-	35
Adriamycin	34	9 (27)	-	45
5-Fluorouracil	24	4 (17)	-	44
Methotrexate	10	1 (10)	-	59

[a] Figures in parentheses are percentages.

ied, none of these options seem to have any clear advantage with respect to response [24,49]. Because of the extensive experience with melphalan (1-phenylalanine mustard) and cyclophosphamide, these drugs have been accepted as standard chemotherapeutic agents with which other new treatment schedules may be compared.

Several non-alkylating drugs could be identified that showed efficacy in ovarian cancer patients. Active anti-tumor agents include antimetabolites (5-fluorouracil, 6-mercaptopurine, methotrexate), vinca alkaloids (vinblastine) and miscellaneous agents such as hexamethylmelamine, *cis*-platinum diamminedichloride (*cis*-platinum), and doxorubicin (adriamycin) [61]. Most of these drugs have been tested in alkylating-agent resistant cases. Results of the studies performed in previously untreated patients are summarized in Table II. Comparative trials have shown hexamethylmelamine and adriamycin to produce a response rate comparable with that of melphalan, whereas 5-fluorouracil seems less active [44,45]. In one randomised trial methotrexate was compared with the alkylating agent Thio-Tepa®. Only one of the initial 10 patients treated with methotrexate alone responded, as compared with 8 out of 12 patients in the Thio-Tepa® group, which suggests that the former drug is less active than alkylating agents [59]. Among the non-alkylating agents *cis*-platinum appears to be at least as effective as alkylating drugs or even more so [11]. It is probably the most active drug producing response rates amounting to 50% (see Table II).

Combination chemotherapy

The use of multiple drugs in combination has given excellent results in the management of several types of tumor. The advantages of combination chemotherapy over single-agent chemotherapy are that a larger cell population will be reached for killing and that there is a broader range of action to prevent growth of resistant cells. For multiple drug regimens, only drugs effective when used alone should be selected. In the ideal case there is no overlapping of toxicity of the drugs in the combinations and it is feasible to use all drugs at their optimal dose and time interval.

Improved results have been obtained with combination chemotherapy for such tumors as malignant lymphoma, breast cancer, and testicular can-

TABLE III

Treatment results obtained with combination chemotherapy without *cis*-platinum in previously untreated patients with advanced ovarian carcinoma[a].

Drug combination	No. of patients evaluable	No. of clinical responses	Median survival (mths)	Reference
CA	101	46 (45)	-	33
Hexa-CAF	28	10 (36)	10	15
MAF	21	7 (33)	-	2
CAF	19	12 (63)	-	2
Hexa-CAF	31	13 (42)	17	37
CHM	120	38 (32)	12	42
H-C	20	10 (50)	14	41
A-C	16	9 (56)	17	41
ThioT-Mtx	14	5 (36)	11	11
HAC	55	43 (78)	-	26
FAC	32	20 (62)	24	40
AC	41	34 (83)	24	38
MECY	21	14 (67)	-	5
FUCY	22	7 (32)	-	5
Hexa-CAF	37	24 (65)	20	48
Hexa-CAF	13	7 (54)	-	28
MF	48	12 (25)	12	39
MF Dact	48	15 (31)	12	39
CF Dact	21	7 (33)	7	39
CAF	71	21 (29)	-	10
Hexa-CAF	40	30 (75)	29	60
MH	97	50 (51)	-	34
CA	72	35 (49)	-	34
CMF	110	45 (41)	17	9
CA	36	13 (36)	12	17
CA	24	17 (71)	14	51
CA	61	22 (36)	13	1
AM	70	44 (63)	17+	50
Total	1289	610 (47)	14[b]	

[a] Figures in parentheses are percentages. See references for detailed information.
[b] Median value.

cer. This led several clinicians to attempt to improve short-term results in ovarian cancer combining effective drugs. A wide variety of combinations have been tested and the results reported in the literature. A compilation of these regimens is given in Tables III and IV. So far, the results in 1289 women treated with combination chemotherapy without *cis*-platinum as initial treatment have been reported. The cumulative response rate for these patients was 47% with a median survival of 14 months. These results do not differ from those reached with alkylating monotherapy (see Table I), which suggests that combination regimens without *cis*-platinum are not superior to melphalan. Indeed, only two investigators found superior long-term results for a combination lacking *cis*-platinum compared

TABLE IV

Treatment results obtained with combination chemotherapy that includes *cis*-platinum in previously untreated patients with advanced ovarian carcinoma[a].

Drug combination	No. of patients evaluable	No. of clinical responses	Median overall survival (mths)	Reference
PACe	35	28 (80)	19	57
CHAP	21	17 (81)	21	23
CAP	91	65 (71)	–	33
PAH	26	10 (38)	–	16
HAP	27	11 (41)	8	6
CAP	23	7 (30)	14	6
DC	19	14 (74)	10	54
PAC	36	30 (83)	21	12
ChIP	32	18 (56)	–	3
ChIAP	35	19 (54)	–	3
PAC-V	8	7 (87)	–	25
PAC	43	28 (65)	–	7
AP	15	12 (80)	19	11
H-CAP	46	44 (96)	19	21
H-FAP	12	11 (92)	13	21
Hexa-CAF-AP	21	12 (57)	–	52
FACP	18	11 (61)	18	40
PAC-I-V	39	24 (61)	23	18
CAP	40	30 (75)	20	48
PC	19	14 (74)	–	54
PAC/HCMF	29	19 (65)	20	64
PAC	36	30 (83)	21	12
CHAD	85	53 (62)	20	53
CHexUP	51	38 (74)	18	62
Total	807	552 (68)	19[b]	

[a] Figures in parentheses are percentages. See references for detailed information.
[b] Median value.

to melphalan in a prospective randomised study [50,60]. But their results were severely criticized [4,14] and could not be confirmed by others [15,17, 34,48,51].

More promising are the results of combination chemotherapy that includes *cis*-platinum (see Table IV). The cumulative response rate of 68% is clearly superior to the response rate of combination chemotherapy regimens lacking this drug (Table III), and the median survival is somewhat longer. The better overall response rate and median survival suggest that the palliative efficacy of the regimens mentioned in Table IV is superior to monochemotherapy or other combinations. This supposition is comfirmed by a number of comparative studies showing significantly prolonged progression-free survival for regimens that include *cis*-platinum [3,11,48,53]. The high proportion of histologically restaged complete remissions is impressive (disappearance of all macroscopical and microscopical disease at second-look laparotomy including biopsies of all suspicious lesions and intraperitoneal washing). Surgical complete remission rates reach values as high as 30%. The patients are potentially long-term survivors and even cured. Comparative randomised studies in a large number of patients

and with a long period of follow-up are mandatory to provide evidence that new chemotherapeutic regimens among the *cis*-platinum combinations will improve survival and may cure more patients.

The CHAP-5 regimen

So far, one of the most powerful combination regimens that have been developed is the four-drug regimen from the Netherlands Joint Study Group for Ovarian Cancer: CHAP-5. The drugs and the method of administration in the CHAP-5 regimen were selected on the basis of several principles. All drugs in the schedule (cyclophosphamide, hexamethylmelamine, adriamycin and *cis*-platinum) are non-crossresistant and are known to be active in ovarian cancer when used alone [20,49,55]. To avoid overlap of toxicity and to ensure that optimum doses could be given, it was decided to administer the drugs as two separate alternating combinations: adriamaycin plus *cis*-platinum (AP) and cyclophosphamide plus hexamethylmelamine (CH). Both combinations alone produce more responses than alkylating monotherapy; moreover, the combination of adriamycin plus *cis*-platinum has been found to be synergistic and to improve overall survival [11,45]. It was felt that it was of major importance to administer the two most active drugs (cyclophosphamide and *cis*-platinum) separately. This ensured that undertreatment would be avoided because proper dosing and a high dose rate could be important factors in improving the treatment results, particularly in the induction period. On the other hand, it is known that there are large individual differences in tolerance to cytostatics. Older women and those who receive more cycles of treatment tolerate the drugs less well [8,29]. Therefore, it was decided that the length of the interval between the courses of adriamycin plus *cis*-platinum and cyclophosphamide plus hexamethylmelamine should be varied according to the dregree of hematological toxicity and individual tolerance. Early in the treatment, when the total cumulative dose of cytostatics is low and the hematological recovery is rapid, the intervals between AP and CH are short (one week). Later on, the planned interval has to be lengthened (up to 6 weeks) because of myelosuppression. With this approach each patient receives in the shortest possible time, the optimum dose of cytotoxic agents she is able to tolerate. The total dose of the cytotoxic agents administered during the first months is much larger than is the case when the drugs are given according to a fixed and less frequent schedule.

In 1979 the Dutch group initiated a randomised study to compare the CHAP-5 regimen to a combination without *cis*-platinum: Hexa-CAF. The Hexa-CAF combination consisted of hexamethylmelamine, cyclophosphamide, methotrexate, and 5-fluorouracil. The regimen is at least as effective as melphalan alone [30,60]. Patients on CHAP-5 received adriamycin 35 mg/m^2 on day 1 as an intravenous bolus injection prior to the administration of *cis*-platinum. *Cis*-platinum 20 mg/m^2 was given intravenously on day 1 through 5. The drug was administered as a 4-h infusion in 1 l of normal saline, immediately following prehydration with 1 l normal saline. Posthydration was obtained with 2 l of normal saline. If diuresis was less than 600 ml per 6 h or the fluid retention more than 1500 ml in 24 h, 5–10 mg furosemide was given intravenously. Starting on day 15, hexamethylmelamine 150 mg/m^2 and cyclophosphamide 100 mg/m^2 were both given orally, daily, for 14 days. In the fifth week no therapy was given. Thereafter, the regimen was repeated starting on day 36 with adriamycin and *cis*-platinum. When myelosuppression occurred, the dosage was modified as shown in Table V.

In a 2-year period, 196 patients were randomised. Of these, 10 patients were not eligible for various reasons. A first report of the study was made with a median follow-up of 29 months [31,32]. Of the patients assigned to the Hexa-CAF regimen, 19% reached a surgically documented complete remission as against 40% in the CHAP-5 group. Despite the administration of therapy, progressive disease was seen in 32% of the Hexa-CAF patients but in only 10% of the patients treated with CHAP-5. As a result the progression-free survival and overall survival curve for CHAP-5 was significantly super-

TABLE V

Protocol for dosage modification of the drugs in the Hexa-CAF and CHAP-5 regimen[a].

Leucocytes (per mm³)	Platelets (per mm³)	Dosage modification (%) ADR	DDP	CYC	HMM	FU	MTX
⩾ 4000	⩾ 120 000	100	100	10'0	100	100	100
3000–4000	75 000–120 000	50	100	50	100	50	50
⩽ 3000	⩽ 75 000	Stop[b]	Stop	Stop	Stop	Stop	Stop

[a] Abbreviations: ADR = adriamycin; DDP = *cis*-platinum; CYC = cyclophosphamide; HMM = hexamethylmelamine; FU = 5-fluorouracil; MTX = methotrexate. Dose must be adjusted weekly during administration.

[b] Stop treatment: after 1 week, reinstitute treatment in case of recovery. After interruption of the cyclophosphamide and hexamethylmelamine, wait for 2 weeks before starting the next treatment cycle with Hexa-CAF and for 1 week before starting CHAP-5. After interruption of the cyclophosphamide and hexamethylmelamine as part of the CHAP-schedule, continue with adriamycin *cis*-platinum in accordance with the above-mentioned instructions.

ior to that for Hexa-CAF ($p = 0.006$). The improved survival of the CHAP-5 group in comparison with the patients who were treated with Hexa-CAF is not due to insufficient second-line treatment of the latter because all patients who failed on Hexa-CAF were offered salvage treatment that included *cis*-platinum.

The toxicity of both regimens was considerable. Of the patients treated with CHAP-5, 55% developed leucopenia with white cell counts below 2000, as against 40% of the patients treated with Hexa-CAF. Peripheral neuropathy occurred in 22% of the Hexa-CAF patients as against in 51% of the CHAP-5 patients; mild paresthesias were encountered in 16%, moderate paresthesias in 32%, and in 4% there were severe paresthesias with marked motor loss. Eighteen percent of the patients on CHAP-5 had to be taken off chemotherapy because of neurotoxicity. Nephrotoxicity was mild. Although 59% of the CHAP-5 patients showed a transient elevation of the serum creatinine level compared with their pre-treatment creatinine, only one patient had to be taken off chemotherapy because of a significant decrease in the glomerular filtration rate. In most patients the dosage of cyclophosphamide and adriamycin had to be reduced because of toxicity. *Cis*-platinum and hexamethylmelamine, however, could be given at nearly full dose. A multivariate analysis revealed that the survival of patients who received the full dosage of hexamethylmelamine as part of the Hexa-CAF schedule was enhanced. Although we have to be careful with conclusions, the relationship may indicate that hexamethylmelamine is a valuable drug as part of the Hexa-CAF regimen. The dosage of the other drugs and the interval between the chemotherapy courses did not have an impact on survival after treatment with either regimen.

The CHAP-5 regimen is the first schedule to result in improved survival times compared with a second combination schedule, i.e. Hexa-CAF, which is at least as good as standard alkylating therapy. We can only speculate on why the CHAP-5 regimen has been so successful, while other studies in which a similar drug combination was used, have failed to show benefit in terms of overall survival.

The Eastern Cooperative Oncology Group used a combination consisting of *cis*-platinum 50 mg/m² intravenously on day 1, adriamycin 25 mg/m² on day 1, cyclophosphamide 600 mg/m² intravenously on day 1 and hexamethylmelamine 150 mg/m² orally on days 8–21 (CHAD). The schedule was repeated after 4 weeks. They compared CHAD prospectively with melphalan. An interim report on their study mentioned a significantly higher response rate for the combination and longer progression-free survival but the authors failed to demonstrate that CHAD prolonged survival significantly [53]. The disparity between their results and those of the Dutch group may be due to the differences in dosage and the method of administration. Patients on CHAP-5 received twice the dose of *cis*-platinum, more adriamycin and more cyclophos-

phamide. Especially the dose of the most active drug in ovarian cancer, *cis*-platinum, could be administered in nearly full dosage (mean 93% of the prescribed dose) throughout the whole treatment. Adriamycin, hexamethylmelamine, and cyclophosphamide could be given in 75%, 82% and 56%, respectively, of the calculated dosage [32]. For adriamycin this means that CHAP-5 patients received a mean of 26 mg/m^2 which is 100% dose of the CHAD schedule. It is uncertain how far the alternation of drugs in the CHAP-5 schedule contributed to the efficacy. Probably a higher dosage of the separate drugs could be administered than when cyclophosphamide, *cis*-platinum and adriamycin were administered simultaneously on the first day as was the case in the CHAD regimen.

It is too early to claim that patients were cured with the CHAP-5 regimen. A 5-year follow-up is mandatory before such a conclusion can be drawn. But long-term results will certainly be superior to those obtained with the Hexa-CAF regimen for two reasons. Firstly, the CHAP-5 regimen produced twice as many histologically complete remissions and these patients have the potential for cure. Secondly, at interim analysis, 70% of the patients treated with CHAP-5 who reached a surgically complete remission at laparotomy, were alive and disease-free with 2 and 3 years of follow-up but only a minority of the patients who reached a complete remission after treatment with Hexa-CAF were disease-free for such a long period after entry.

In conclusion, it can be said that the CHAP-5 regimen is probably one of the most effective regimens currently available for the initial treatment of ovarian cancer. Further improvement of the treatment results will be difficult and large randomised trials will be necessary to document further progress.

Future clinical research

Because no effective new drugs are available which justify a trial as a first-line treatment, we must try to decrease the toxicity and the morbidity of the CHAP-5 schedule without reducing efficacy and survival. A first logical step would be to diminish the number of cytotoxic drugs in the schedule. Unfortunately, there are no large well-documented studies in the literature which deal with the question of which drugs could be omitted. Conclusions about the effects of drugs are reached purely on the basis of the difference in the number of surgically documented complete remissions and the number of patients that survive. Therefore, the Netherlands Joint Study Group of Ovarian Cancer performed a study which compared the results of CHAP-5 and a combination of cyclophosphamide 750 mg/m^2 and *cis*-platinum 75 mg/m^2, both having been administered intravenously on day 1 (CP). The schedule was repeated after 3 weeks. The CP regimen was chosen because the group was not aware of studies which indicated that the addition of adriamycin or hexamethylmelamine would improve the results obtained with an alkylating agent alone or any other combination [24,56]. Although adequate hydration occurred, a preliminary analysis of this study showed that the CP regimen was probably more nephrotoxic than CHAP-5. After a median follow-up of 1 year, 22 patients treated with CP had to be taken off chemotherapy with CP because of nephrotoxicity. So far no differences in survival have been detected. Possibly limiting the number of treatment cycles for the CP-treated patients due to nephrotoxicity will have no impact on the survival and the treatment outcome. Long-term results are needed before we can draw definite conclusions. With regard to the problem of nephrotoxicity the replacement of *cis*-platinum by a less toxic *cis*-platinum analogue may be an attractive alternative for future study. Currently the Dutch group is testing carboplatinum as an alternative for *cis*-platinum in the CHAP-5 combination.

Another possible way of decreasing the side effects and morbidity of the CHAP-5 treatment is to limit the total number of cycles. Because the main toxicity of CHAP-5 occurs after 6 treatment cycles and complete remissions in most cases were reached before the 7th cycle, a logical step would be to investigate whether treatment outcome after 6 cycles is as good as the outcome after treatment of 9–12 courses.

It is hoped that the outcome of the above-mentioned studies and of the research projects being conducted elsewhere will lead to less toxicity and morbidity for our patients and that new drugs will be available soon to be incorporated in the present treatment schedules.

References

1 Alberts, D. S., Moon, T. E., Stephens, R. A., et al. Randomized study of chemoimmunotherapy for advanced ovarian carcinoma: a preliminary report of a southwest oncology group study. Cancer Treat. Rep. 63: 325-331, 1979.

2 Aroney, R. S., Levi, J. A. and Dalley, D. N. Triple drug chemotherapy for advanced ovarian carcinoma: comparative study of two regimens. Med. J. Aust. 1: 633-635, 1981.

3 Barker, G. H. and Wiltshaw, E. Randomized trial comparing low-dose cisplatin and chlorambucil with low-dose cisplatin, chlorambucil, and doxorubicin in advanced ovarian carcinoma. The Lancet 1: 747-750, 1981.

4 Barlow, J. J. and Blumenson, L. E. Therapy of advanced ovarian carcinoma. Letter to the editor. New Engl. J. Med. 22: 676, 1979.

5 Barlow, J. J., Piver, M. S. and Lele, S. B. High-dose methotrexate with rescue plus cyclophosphamide as initial chemotherapy in ovarian adenocarcinoma. Cancer 46: 1333-1338, 1980.

6 Bernath, A., Andrews, T. A., Dixon, R. H., et al. Long term follow-up of HAP (hexamethylmelamine, adriamycin, cis-platinum) vs CAP (cyclophosphamide, adriamycin, cis-platinum) in alkylating agent resistant advanced ovarian carcinoma. Proc. Am. Soc. Clin. Oncol. 1: 110, 1982.

7 Bolis, G., Sessa, C., Mohna, P., et al. Cis-platinum (P), adriamycin (A), and cyclophosphamide (C) in combination for previously untreated advanced ovarian cancer. Conference UICC conference on Clinical Oncology, 107, 1981.

8 Bonadonna, G. and Valagussa, P. Dose-response effect of adjuvant chemotherapy in breast cancer. N. Engl. J. Med. 304: 10-15, 1981.

9 Brodovsky, H. S., Temkin, N. and Sears, M. Melphalan versus cyclophosphamide methotrexate and 5-fluorouracil in women with ovarian cancer. Proc. Am. Clin. Oncol. 18: 308, 1977.

10 Bruckner, H. W., Pagano, M. and Falkson, G. Controlled prospective trial of combination chemotherapy with cyclophosphamide, adriamycin and 5-fluorouracil for the treatment of advanced ovarian cancer: a preliminary report. Cancer Treat. Rep. 63: 297-299, 1979.

11 Bruckner, H. W., Cohen, C. J., Goldberg, J. D., et al. Improved chemotherapy for ovarian cancer with cis-diamminedichloroplatinum and adriamycin. Cancer 47: 2288-2294, 1981.

12 Budd, G. T., Livingston, R. B., Webster, K., et al. Treatment of advanced ovarian cancer with cis-platin, adriamycin and cytoxan (PAC), Proc. Am. Soc. Clin. Oncol. 1: 117, 1982.

13 Van Bunningen, B. N. F. M. Radiotherapie van het ovariumcarcinoom. In: Het Ovariumcarcinoom, pp. 93-108. Editors: J. W. Barents et al. Stafleu's Wetenschappelijke Uitgevermaatschappij, Alphen aan de Rijn, 1983.

14 Bush, R. S. Therapy of advanced ovarian carcinoma. Letter to the editor. N. Engl. J. Med. 22: 676, 1979.

15 Carmo-Pereira, J., Costa, F. O., Henriques, E., et al. Advanced ovarian carcinoma: a prospective and randomized clinical trial of cyclophosphamide versus combination cytotoxic chemotherapy (Hexa-CAF). Cancer 48: 1947-1957, 1981.

16 Carmo-Pereira, J., Costa F. O. and Henriques, E. Cis-platinum (P), adriamycin (A), and hexamethylmelamine (H) vs cyclophosphamide (C) in advanced ovarian carcinoma – a randomized study. Proc. Am. Soc. Clin. Oncol. 1: 107, 1982.

17 Edmonson, J. H., Flemming, T. R., Decker, D. G., et al. Different chemotherapeutic sensitivities and host factors affecting prognosis in advanced ovarian carcinoma versus minimal residual disease. Cancer Treat. Rep. 63: 241-247, 1979.

18 Ehrlich, C. E., Einhorn, L., Williams, D., et al. Chemotherapy for stage III-IV epithelial ovarian cancer with cis-dichlorodiammineplatinum(II), adriamycin, and cyclophosphamide; a preliminary report. Cancer Treat. Resp. 63: 281-288, 1979.

19 Fuks, Z. External radiotherapy of ovarian cancer: standard approaches and new frontiers. Semin. Oncol. 2: 252-266, 1975.

20 Gershenson, D. M., Wharton, J. T., Herson, J., et al. Single-agent cis-platinum therapy for advanced ovarian cancer. Obstet. Gynecol. 58: 487-496, 1981.

21 Greco, F. A., Julian, C. G., Richardson, R. L., et al. Advanced ovarian cancer: brief intensive combination chemotherapy and second-look operation. Obstet. Gynecol. 58: 199-205, 1981.

22 Hall, D. J., Diasio, R. and Goplerud, D. R. Cis-platinum in gynaecologic cancer. I. Epithelial ovarian cancer. Am. J. Obstet. Gynecol. 141: 299-304, 1981.

23 Harvey, H. A., Lipton, A., Summonds, M., et al. A randomized trial of alkeran versus cyclophosphamide, hexamethylmelamine, adriamycin and cis-platinum combination chemotherapy in advanced ovarian carcinoma. Clin. Res. 30(2): 418A (Abstr.), 1982.

24 Katz, M. F., Schwartz, P. E., Kapp, D. S., et al. Epithelial carcinoma of the ovary: current strategies. Ann. Int. Med. 95: 98-111, 1981.

25 Kenemans, P., Verheyen, R., Pieters, G., et al. Combination therapy with cis-platinum, cyclophosphamide and adriamycin in the treatment of advanced ovarian cancer. Conference Book UICC Conference on Clinical Oncology, 105, 1981.

26 Mangioni, C., Bolis, G., Valente, I., et al. Cis-diamminechloroplatinum, adriamycin, cyclophosphamide (PAC) vs hexamethylmelamine, adriamycin, and cyclophosphamide (HAC) in advanced ovarian cancer. Proc. Am. Soc. Clin. Oncol. 22: 166, 1981.

27 Masterson, J. P. and Nelson, J. H. The role of chemotherapy in the treatment of gynaecologic malignancy. Am. J. Obstet. Gynecol. 93: 1102–1111, 1965.

28 Mendiola, C., Quiben, R., Hernandez, V., et al. Combination chemotherapy of advanced ovarian carcinoma with hexamethylmelamine, cyclophosphamide, methotrexate and fluorouracil (Hexa-CAF). Cancer Chemother. Pharmacol. 5: 33, 1980.

29 Neijt, J. P., van Lindert, A. C. M., Vendrik, C. P. J., et al. Hexa-CAF combination chemotherapy and other multiple-drug regimens in advanced ovarian carcinoma: present and future. Neth. J. Med. 22: 38–44, 1979.

30 Neijt, J. P., van Lindert, A. C. M., Vendrik, C. P. J., et al. Treatment of advanced ovarian carcinoma with a combination of hexamethylmelamine, cyclophosphamide, methotrexate, and 5-fluorouracil (Hexa-CAF) in patients with and without previous treatment. Cancer Treat. Rep. 64: 323–326, 1980.

31 Neijt, J. P., Ten Bokkel Huinink, W. W., Hamerlynck, J. V. T. H., van der Burg, M. E. L., van Lent, M., van Lindert, A. C. M., van Oosterom, A. T., Heintz, A. P. M., Vriesendorp, R., Bouma, J. and Pinedo, H. M. Surgery and combination chemotherapy with Hexa-CAF and CHAP-5 in FIGO-stages III and IV ovarian carcinoma (Abstr.). 2nd European Conference on Clinical Oncology, 163, 1983.

32 Neijt, J. P. Combination Chemotherapy in the Treatment of Advanced Ovarian Carcinoma. Thesis. ICG Printing, Dordrecht, The Netherlands, 1983.

33 Omura, G. A., Ehrlich, C. G. and Blessing, J. A. A randomized trial of cyclophosphamide (C) plus adriamycin (A) with or without cis-platinum (P) in ovarian carcinoma. Proc. Am. Soc. Clin. Oncol. 1: 104, 1982.

34 Omura, G. A., Blessing, J. A., Morrow, C. P., et al. Follow-up on a randomized trial of melphalan vs melphalan plus hexamethylmelamine vs adriamycine plus cyclophosphamide in advanced ovarian adenocarcinoma. Proc. Am. Soc. Clin. Oncol. 22: 470, 1981.

35 De Palo, G. M., De Lena, M., Di Re, F., et al. Melphalan versus adriamycin in the treatment of advanced carcinoma of the ovary. Surg. Gynecol. Obstet. 141: 899–902, 1975.

36 De Palo, G. M., De Lena, M. and Bonadonna, G. Adriamycin versus adriamycin plus melphalan in advanced ovarian carcinoma. Cancer Treat. Rep. 61: 355–357, 1977.

37 De Palo, G., Demicheli, R. and Valagussa, P. Prospective study with Hexa-CAF combination in ovarian carcinoma. Cancer Chemother. Pharmacol. 5: 157–161, 1981.

38 Parker, L. M., Griffiths, C. T., Yankee, R. A., et al. Combination chemotherapy with adriamycin-cyclophosphamide for advanced ovarian carcinoma. Cancer 46: 669–674, 1980.

39 Park, R. C., Usa, M. C. and Blom, J. Treatment of women with disseminated or recurrent advanced ovarian cancer with melphalan alone in combination with 5-fluorouracil and dactinomycin or with the combination of cytoxan, 5-fluorouracil and dactinomycin. Cancer 45: 2529–2542, 1980.

40 Pouillart, P., Palangie, T., Bretaudeau, B., et al. Role of Cis-DDP in a combination of chemotherapy in patients with ovarian carcinoma, stage III and IV. Conference Book UICC Conference on Clinical Oncology, 109, 1981.

41 Schwartz, P. E., Lawrence, R. and Katz, M. Combination chemotherapy for advanced ovarian cancer: a prospective randomized trial comparing hexamethylmelamine and cyclophosphamide to doxorubicin and cyclophosphamide. Cancer Treat. Rep. 65: 137–141, 1981.

42 Scot, J. S. For the Medical Research Council's Working Party on Ovarian Cancer. Medical research council study of chemotherapy in advanced ovarian cancer. Br. J. Obstet Gynaecol. 88: 1174–1185, 1981.

43 Smith, J. P., Rutledge, F. and Wharton, J. T Chemotherapy of ovarian cancer. New approaches to treatment. Cancer 30: 1565–1571, 1972.

44 Smith, J. P. and Rutledge, F. N. Random study of hexamethylmelamine, 5-fluorouracil, and melphalan in treatment of advanced ovarian carcinoma of the ovary. Natl. Cancer Inst. Monogr. 42: 169–172, 1975.

45 Smith, J. P. Chemotherapy in gynaecologic cancer. Surg Clin. North Am. 58: 201–215, 1978.

46 Smith, J. P. and Day, G. T. Review of ovarian cancer at the University of Texas Systems Cancer Center M. D. Anderson Hospital and Tumor institute. Am. J. Obstet. Gynecol. 135: 984–990, 1979.

47 Stanhope, C. R., Smith, J. P. and Rutledge, F. Second tri drugs in ovarian cancer. Gynecol. Oncol. 5: 52–58, 1977.

48 Sturgeon, J. F. G., Fines, S., Gospodarowicz, M. K., et a A randomized trial of melphalan alone versus combinatic chemotherapy in advanced ovarian cancer. Proc. Am. So Clin. Oncol. 1: 108, 1982.

49 Tobias, J. S. and Griffiths, C. T. Management of ovari carcinoma. N. Engl. J. Med. 294: 817–823, 1976.

50 Tropé, C. A prospective and randomized trial comparis of melphalan vs adriamycin-melphalan in advanced ovari carcinoma. Proc. Am. Assoc. Clin. Oncol. 22: 469, 1981.

51 Turbow, M. M., Jones, H., Yu, V. K., et Chemotherapy of ovarian carcinoma. A comparison of m phalan vs adriamycin-cyclophosphamide. Proc. Am. Ass Cancer Res. 21: 196, 1980.

52 Varini, M., Geiger, V., Preitner, J., et al. Hexa-CAF (h amethylmelamine, cyclophosphamide, methotrexate, fl rouracil) alternated with DDP/ADM (cisplatin, adriabl tine) in the treatment of advanced carcinoma of the ova Tumori 67: 70, 1981.

53 Vogl, S. E., Kaplan, B. and Pagano, Diamminedichloroplatinum (D)-based combination che otherapy (CT) is superior to melphalan (M) for advan ovarian cancer (OvCa) when age is $\geqslant 50$ and tumor diar

ter >2 cm. Proc. Am. Soc. Clin. Oncol. 1: 119, 1982.

54 Wernz, J. C., Speyer, J. L., Noumoff, J., et al. Cisplatinum (DDP)/cytoxan: a high dose DDP regimen for advanced ovarian carcinoma. Proc. Am. Soc. Clin. Oncol. 1: 112, 1982.

55 Wharton, J. T., Rutledge, F., Smith, J. P., et al. Hexamethylmelamine: an evaluation of its role in the treatment of ovarian cancer. Am. J. Obstet. Gynecol. 133: 833–844, 1979.

56 Wharton, J. T., Herson, J., Edwards, C. L., et al. Long-term survival following chemotherapy for advanced epithelial ovarian carcinoma. In: Therapeutic Progress in Ovarian Cancer, Testicular Cancer and the Sarcomas, pp. 95–112. Editors: A. T. van Oosterom et al. Martinus Nijhoff Publishers, The Hague, 1980.

57 Williams, C. J., Mead, B., Arnold, A., et al. Chemotherapy of advanced ovarian carcinoma: initial experience using a platinum-based combination. Cancer 49: 1778–1783, 1982.

58 Willson, J. K. V., Ozols, R. F., Lewis, B. J., et al. Current status of therapeutic modalities for treatment of gynecologic malignancies with emphasis on chemotherapy. Am. J. Obstet. Gynecol. 141: 81–98, 1981.

59 Young, R. C. Chemotherapy of ovarian cancer: past and present. Semin. Oncol. 2: 267–276, 1975.

60 Young, R. C., Chabner, B. A., Hubbard, S. P., et al. Prospective trial of Melphalan (L-PAM) versus combination chemotherapy (Hexa-CAF) in ovarian adenocarcinoma. N. Engl. J. Med. 299: 1261–1266, 1978.

61 Young, R. C. Gynaecologic malignancies. In: Cancer Chemotherapy 1979. The EORTC Cancer Chemotherapy Annual 1, pp. 340–375. Editor: H. M. Pinedo. Excerpta Medica, Amsterdam, 1979.

62 Young, R. C., Howser, D. M. and Myers, C. E. Combination chemotherapy (CHex-UP) with intraperitoneal maintenance in advanced ovarian adenocarcinoma. Proc. Am. Soc. Clin. Oncol. 22: 465, 1981.

63 Young, R. C., Canellos, G. P., Chabner, B. A., et al. Chemotherapy of advanced ovarian carcinoma: a prospective comparison of phenylalanine mustard and high dose cyclophosphamide. Gynecol. Oncol. 2: 489–497, 1974.

64 Young, Y. A., Kroener, J. F., Lucas, W. E., et al. Cisplatin (P), adriamycin (Adr), and cyclophosphamide (Ctx) alternating with hexamethylmelamine (Hmm), Ctx, methotrexate (Mtx), and 5-fluorouracil (5-FU) for advanced ovary cancer (Adoc). Proc. Am. Soc. Clin. Oncol. 1: 115, 1982.