Eur J Cancer Clin Oncol, Vol. 21, No. 4, pp. 475–481, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

A Randomized Study of Single Agent vs Combination Chemotherapy in FIGO Stages II_B, III and IV Ovarian Adenocarcinoma

KRISTIAN AABO,*† INGE HALD,* STEEN HØRBOV,‡ PER DOMBERNOWSKY,‡§ HEINE H. HANSEN,* HILDA M. SØRENSEN,* FINN LUNDVALL,|| NIELS C. NIELSEN‡ and BENT I. SØRENSEN*

*Departments of Chemotherapy, Gynecologic Oncology and Surgery, Finsen Institute, Copenhagen, Denmark, ‡Departments of Internal Medicine C and Gynecology, Bispebjerg Hospital, Copenhagen, Denmark and ||Department of Gynecology, Hvidovre Hospital, Copenhagen, Denmark

Abstract—*From* 1977 *until* 1980, 179 *patients with newly diagnosed FIGO stages* II_B, *III or IV ovarian adenocarcinoma were randomized in a two-armed clinical trial: dihydroxybusulfan* (*B*) 600 mg/m² *p.o. for* 4–6 weeks *q* 12 weeks *or cyclophosphamide* (*C*) 150 mg/m² *p.o. for* 7 days *q* 4 weeks *vs a combination of cyclophosphamide* 400 mg/m² *i.v., doxorubicin* 30 mg/m² *and* 5-*fluorouracil* 400 mg/m² *i.v., days* 1 *and* 8 *q* 4 weeks (*CAF*). *In addition, stage* II_B *patients were randomised to* ± *pelvic irradiation. The patients were stratified according to anatomic stage. The treatment groups were comparable with respect to performance status, age and histology. Twenty-three patients were excluded because of protocol violation, leaving* 156 *patients evaluable for survival with an observation period of* 3–6 yr. *Twenty patients were in stage* II_B, *while the remaining* 136 *patients were classified as stages III and IV. No statistically significant difference was found in survival or response between the two single agents. The overall median response rate* (*single drug*: 27%; *CAF*: 47%) *and the median response duration* (*single drug*: 5 months; *CAF*: 10 months) *were significantly superior for the CAF group compared to the single agent group. No statistical difference in median survival was observed between single-drug treatment* (12 months) *and CAF* (14 months), *despite the fact that responders lived significantly longer than non-responders* (17 *vs* 10 months). *In stage* II_B *patients receiving chemotherapy no benefit of pelvic irradiation was found. Thirty patients* (19%) *underwent second-look laparotomy, with* 15 (50%) *being completely free of disease. So far only one patient* (7%) *has relapsed. Two additional patients, who had microscopic disease removed at second-look laparotomy, seem to have been rescued by this procedure.*

INTRODUCTION

MANY non-controlled studies on the effect of single-drug chemotherapy in advanced ovarian carcinoma have shown activity of various agents, particularly of alkylating agents [1, 2]. In 1978 Young *et al.* [3] reported on the superiority of combination chemotherapy (hexamethylmelamine, cyclophosphamide, methotrexate and 5-flourouracil: hexa-CAF) compared to a single alkylating agent (melphalan) with regard to both response rate and median survival. In an attempt to test the same concept in patients with inoperable ovarian carcinoma we carried out a randomized study from 1977 until 1980 on newly diagnosed patients. The prime purpose was to compare the therapeutic effect of a single alkylating agent with combination chemotherapy using response rate, response duration and survival as therapeutic parameters. Secondly, we wanted to examine whether, with respect to activity, cyclophosphamide was comparable with dihydroxybusulfan, which traditionally has been the drug of choice among alkylating agents for the treatment of ovarian cancer in Denmark. As dihydroxybusulfan has been associated with a

Accepted 18 October 1984.
†To whom requests for reprints should be addressed at: Department of Chemotherapy, Finsen Institute, 49 Strandboulevarden, DK-2100 Copenhagen, Denmark.
§Present address: Department of Oncology, Copenhagen County Hospital, Herlev, Denmark.

rather high incidence of acute myeloid leukemia after long-term treatment [4], it would be preferable to replace this drug with another alkylating agent exhibiting similar activity but with a lower leukemogenic effect. Finally, the effect of pelvic irradiation in FIGO stage II_B was examined.

MATERIALS AND METHODS

Patients with histologically verified ovarian carcinoma according to the WHO classification [5] and in FIGO (International Federation of Gynecology and Obstetrics) stages II_B, III and IV were eligible. Other inclusion criteria were: age ≤ 70 yr, no previous malignant disease, a time interval of less than 6 weeks from diagnostic surgery to start of protocol treatment, no prior radiation or chemotherapy, an expected survival of more than 2 months and normal kidney, heart, liver and bone marrow functions.

Disease evaluable for response included distinct palpable abdominal or pelvic masses, peripheral lymph nodes and parenchymal lung and skin metastases. Malignant pleural effusion, ascites, bone or cerebral metastases were not considered evaluable parameters, if they were the sole location of metastatic spread. Response was defined according to the WHO criteria [6]. Response duration was calculated in months from the beginning of detected tumor regression until the beginning of detected progression. Survival was calculated in months from start of protocol treatment.

Disease status was evaluated by physical and pelvic examinations and chest X-ray every 4-6 weeks. In selected cases supplementary abdominal and pelvic ultrasound were performed. If possible, peritoneoscopy or second-look laparotomy was performed after 12-18 months of treatment, if a significant clinical response was obtained. During second-look laparotomy biopsies from suspicious lesions, adhesions or fibrous tissue, multiple random peritoneal biopsies, diaphragmatic scrapings and washings of the 'cul-de-sac' for cytologic examination were performed. If not done at primary surgery, hysterectomy, bilateral salpingooophorectomy and omentectomy were done, if possible.

If malignant tissue was present but significantly reduced at second-look operation, the patient was treated until clinical progression with the same regimen. Doxorubicin was omitted if the total dose of 550 mg/m^2 had been achieved. If the patient was in complete remission, no further treatment was given, and the patient was followed every 2-3 months with physical and pelvic examinations.

The patients were stratified according to anatomic stage and subsequently randomized to either single-drug or combination chemotherapy. Stage II_B patients were furthermore randomized to either pelvic irradiation or no radiation therapy. Patients in the single-drug group received either dihydroxybusulfan (B) 600 mg/m^2 p.o. 4-6 weeks q 10-12 weeks or cyclophosphamide (C) 150 mg/m^2 p.o. $\times$ 7 days q 4 weeks. Owing to differences in the ability to recruit patients and to differences in previous treatment policy between the participating departments, the patients who were randomized to single-drug treatment were subsequently randomized to cyclophosphamide or dihydroxybusulfan with a 2:1 preference. The combination chemotherapy consisted of cyclophosphamide 400 mg/m^2 i.v., doxorubicin 30 mg/m^2 i.v. and 5-fluorouracil 400 mg/m^2 i.v. days 1 and 8 q 4 weeks (CAF). The total cumulative dose of doxorubicin was not to exceed 550 mg/m^2. Pelvic irradiation was administered as supervoltage X-rays (linear accelerator) or cobalt 60 on opposing parallel anterior and posterior fields. The upper field limit was the fourth lumbar vertebra, the lower limit extended to the inferior edge of the symfysis. A total dose of 45-50 Gy was delivered over 5-6 weeks. Irradiation was started 4 weeks after initiation of chemotherapy.

The blood counts were performed days 1 and 8 q 4 weeks, and if the treatment was postponed, every week until chemotherapy could be restarted. If the WBC was $>3.0 \times 10^9$/l and the platelet count was $>100 \times 10^9$/l, the drugs were given in 100% dosage. The dose of the cytotoxic drugs was reduced to 66% if the WBC was $2.0\text{-}3.0 \times 10^9$/l and/or the platelets were $75\text{-}100 \times 10^9$/l. If the blood counts were below these figures the therapy was postponed and restarted as a 66% dosage, when the WBC was $>3.0 \times 10^9$/l and the platelets were $>100 \times 10^9$/l.

If progression occurred, the patients subsequently received either experimental medical treatment [7-9] and/or radiotherapy or other palliative therapy, depending on the clinical status.

RESULTS

The patients have been observed for 3-6 yr since the start of treatment. One hundred and seventy-nine patients were randomized. Twenty-three patients were excluded because of protocol violations, including a too-long lag period from diagnostic surgery until start of chemotherapy in three patients, other previous malignancy in four patients, uncertain diagnosis in eight patients, wrong stage in seven patients and treatment refusal in one patient.

Among the 156 evaluable patients, 68 received single-drug and 88 combination chemotherapy. The two groups were comparable regarding anatomic stage, histology, surgical procedure, performance status and age (Table 1). The median performance status (WHO) was 1 (range 0–4) and the median age was 58 yr (range 28–70 yr). Sixteen patients had metastases to the liver, seven to the pleura, seven to extra-abdominal lymph nodes and one to the lung.

Table 1. Characteristics of the 156 evaluable patients treated for stages II_B, III and IV carcinoma

	Single drug	CAF	Total	(%)
No pts randomized	82	97	179	
No pts evaluable	68	88	156	
FIGO stage				
II_B	12	8	20	(13)
III minimal	6	15	21	(13)
III extensive	38	46	84	(54)
IV	12	19	31	(20)
Histology				
Serous	30	42	72	(47)
Mucinous	3	8	11	(7)
Endometrioid	1	3	4	(3)
Clear cell	0	0	0	(0)
Mixed epithelial	0	4	4	(3)
Low differentiated	34	31	65	(40)
Surgery				
Biopsy only	23	27	50	(32)
OM	3	8	11	(7)
USO/BSO	9	17	26	(17)
USO/BSO+OM	9	8	17	(11)
TAH/PAH+BSO	10	15	27	(17)
TAH/PAH+BSO+OM	14	13	25	(16)
Bowel resection			4	(3)

OM: omentectomy; USO: unilateral salpingooophorectomy; BSO: bilateral salpingooophorectomy; TAH: total abdominal hysterectomy; PAH: partial abdominal hysterectomy.

Response

Among the 156 evaluable patients, 23 received dihydroxybusulfan, 45 cyclophosphamide and 88 combination chemotherapy (CAF). Sixty-eight percent of the patients had measurable disease evaluable for response (48 patients in the single-drug group and 58 patients in the CAF group). No difference was observed in response rates or survival between the two single-drug regimens, justifying a unification of these data into one group. The overall median response rate (single drug: 27%; CAF: 47%) and the median response duration (single drug: 5 months; CAF: 10 months) were significantly higher and longer for the CAF group than for the single-drug group ($P < 0.05$) (Table 2). Also, the complete response rate was higher in the combination arm (24 vs 13%). Tumors with serous histology responded more frequently (50%) than tumors with poorly differentiated histology (29%). Four patients in the single-drug arm and two patients in the CAF arm benefited from a second-line treatment, which may have affected survival. In this respect, however, the two treatment arms are comparable, as there are only two long-lasting ongoing complete responses, one in each group.

Survival

One hundred and twenty-eight patients (82%) have died, leaving 23 (15%) alive without disease and five alive with disease (Table 2). All but one patient, who died of acute myocardial infarction and at autopsy was in complete remission, died of malignant disease. There was no statistical difference between the single-drug and the CAF treatment regarding survival (single-drug: median 12 months; CAF: median 14 months) (Fig. 2), despite the fact that responders lived significantly ($P < 0.001$) longer than non-responders (median 17 vs 10 months) (Fig. 3). Of the 20 patients with stage II_B disease, 11 received supplemental pelvic irradiation. There was no difference regarding survival between patients receiving pelvic irradiation and patients who did not. Similarly, there was no difference in survival regarding histologic subtypes. Stage II_B and stage III minimal residual disease (tumor volume less than 1–2 cm^3) had a far better prognosis than stage III extensive residual disease (more than 2 cm^3 tumor volume) and stage IV (median survival 47 vs 12 months, $P < 0.001$) (Fig. 4). No statistical difference was observed between stage II_B and stage III minimal or between stage III extensive and stage IV. Of the patients alive without disease 19/23 (83%) were stages II_B and III minimal. Among the 23 patients alive without disease 12 had residual disease after primary laparotomy (three extensive) and seem subsequently to have been cleared for tumor by chemotherapy.

Second-look laparotomy

Thirty patients (19%) underwent second-look laparotomy (Table 3). Fifteen (50%) were macroscopically and microscopically in complete remission, including 36% of the patients with stage II_B and stage III minimal disease compared to only 0.9% of the patients with stage III extensive and stage IV. The frequency of patients reaching second-look laparotomy was highest in the CAF group, corresponding to the higher response rate. Two of four patients having microscopic disease in internal genitalial organs removed at second-

Table 2. Response and survival data in ovarian patients treated with single-drug (dihydroxybusulfan or cyclophosphamide) or combination chemotherapy (cyclophosphamide, doxorubicin and 5-fluorouracil, CAF)

Response	Single drug No. of pts	(%)	CAF No. of pts	(%)	Total No. of pts	(%)
Evaluable	48	(71)	58	(66)	106	(68)
CR	6	(13)	14	(24)	20	(19)
		(27)		(47)		
PR	7	(14)	13	(23)	20	(19)
Median response duraion in months (range)	5 (2-57+)		10 (2½-71)			
Survival						
Evaluable	68		88		156	
Dead	58	(85)	70	(80)	128	(82)
Alive:						
-disease	9	(13)	14	(16)	23	(15)
+disease	1	(2)	4	(4)	5	(3)
Median survival in months (range)	12 (2-60+)		14 (1-73+)			

CR: complete response; PR: partial response.

look laparotomy are alive and free of disease with an observation period of 59 and 40 months. None of the patients with macroscopic disease at second look have been surgically rescued. Only one (7%) of the patients who were completely disease-free at re-exploration has relapsed.

Toxicity

One patient (1.5%) in the single-drug group and seven (8%) in the CAF group refused to complete protocol treatment owing to subjective side-effects, in particular gastrointestinal toxicity. As shown in Table 4, dihydroxybusulfan was the most myelotoxic whereas cyclophosphamide had

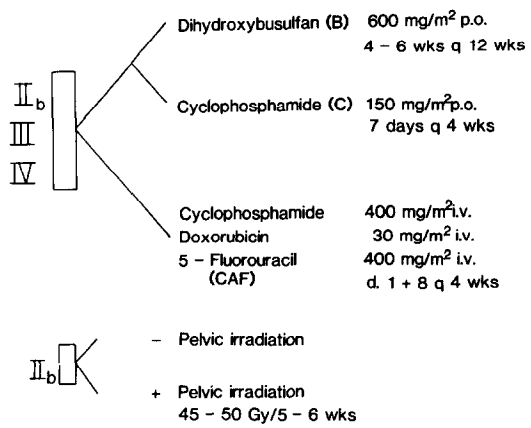

Fig. 1. Study design.

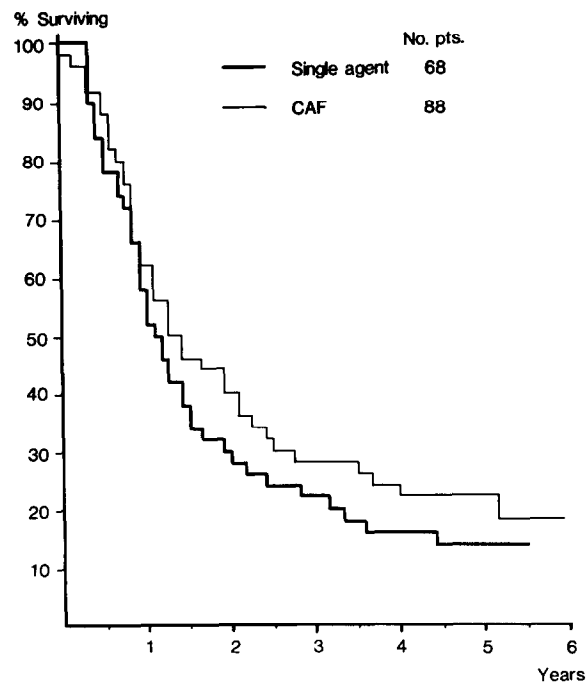

Fig. 2. Actuarial survival probability by treatment category. There was no significant difference between single-agent and combination chemotherapy (chi-square: 1.49403, P > 0.10).

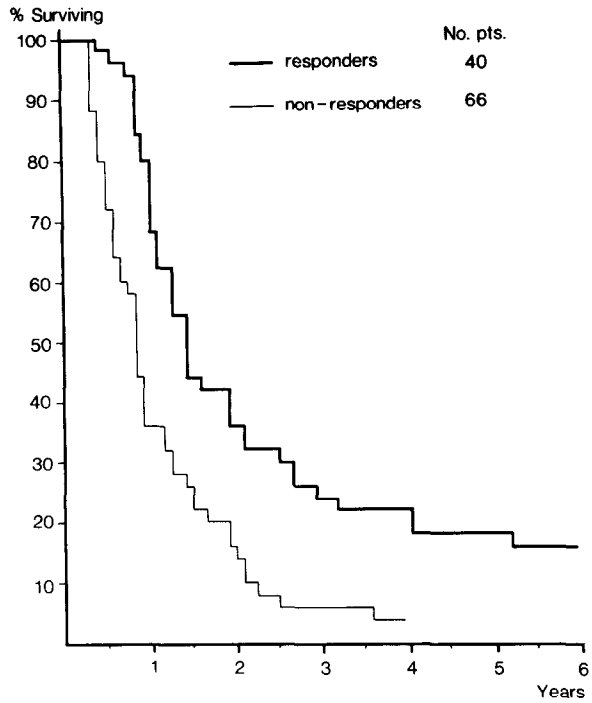

Fig. 3. Actuarial survival probability by response category. Responders (median survival 17 months) *had a significantly better prognosis than non-responders (median survival* 10 months) *(chi-square:* 14.6604, $P < 0.001$).

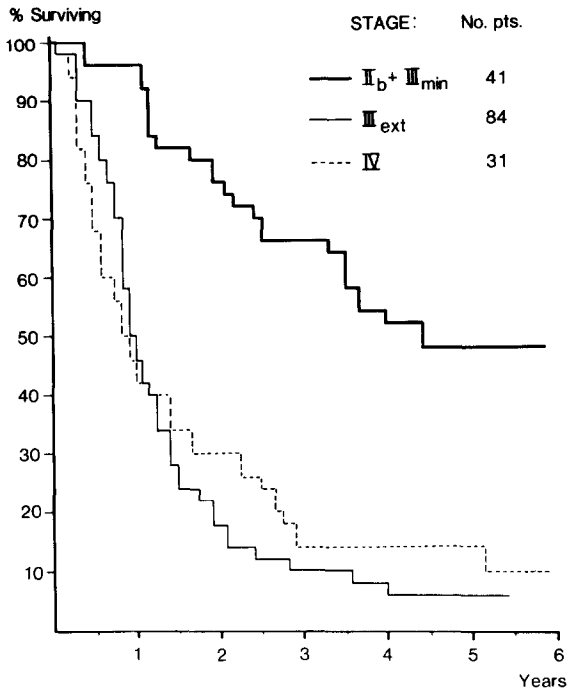

Fig. 4. Actuarial survival probability by initial stage. Stages IIB and III minimal residual disease (median survival 47 months) *had a significantly better prognosis than stages III extensive and IV patients (median survival* 12 months) *(chi-square:* 38.2537, $P < 0.001$).

less effect on the bone marrow. Regarding subjective side-effects, CAF had the most pronounced effect on emesis and hair loss. Thirty-six patients received between 500 and 550 mg/m^2 of doxorubicin. None developed symptoms or signs of cardiomyopathy. The side-effects induced by pelvic irradiation were mainly diarrhea and frequent and painful urination.

DISCUSSION

With a minimal observation time of 3 yr after admission of the last patient to the trial we have not been able to show that combination chemotherapy including cyclophosphamide, doxorubicin and 5-fluorouracil was better than a single alkylating agent concerning survival. In three randomized studies comparing a single alkylating agent with the combination of cyclophosphamide and doxorubicin the median survival was 12-14 months, with no significant difference between the two treatment arms, the same as the results of our study [10-12]. Similar median survival rates have been found in other studies comparing single alkylating agents to various combinations [13-15]. So far, only the study of Young *et al.* [3] has demonstrated a better median survival in patients treated with combination chemotherapy compared to patients treated with a single agent (29 vs 17 months). The latter study has also demonstrated a higher overall response rate (single alkylating agent 54% vs hexa-CAF 76%) than the majority of other studies including more than 20 patients in each treatment

Table 3. Second-look laparotomy data in ovarian cancer patients treated with chemotherapy

Second look	Single drug No. of pts	(%)	CAF No. of pts	(%)	Total No. of pts	(%)
Total	9/68	(13)	21/88	(24)	30/156	(19)
-disease	5	(7)	10	(11)	15	(10)
Microscopic disease	2		2		4	
Macroscopic disease	2		9		11	

Table 4. Toxicity of the chemotherapeutic regimens used in the treatment of ovarian cancer patients

	Dihydroxybusulfan	Cyclophosphamide	CAF
WBC × 10^9/l			
Median	2.0	3.6	2.6
Lowest	0.4	1.1	0.4
Plts × 10^9/l			
Median	70	241	168
Lowest	7	109	13
Hb mmol/l			
Median	6.1	6.9	6.4
Lowest	4.7	5.7	4.7
No. of pts with fever and leukopenia	1	0	3
No. of pts with bleedings	4	0	1
Pts receiving blood transfusions	50%	20%	35%
Nausea-vomiting	rare	moderate	frequent
Alopecia	rare	rare	always
Stomatitis	4	1	2
Diarrhea	0	0	4
Various	1	0	4

arm [10-17]. In these the overall response rate for a single alkylating agent varied from 11 to 40% and for combination chemotherapy from 30 to 50%, which is close to the findings in our study. This may be explained by the differences in the combinations of drugs used; however, factors such as selection of patients, intensity of treatment and evaluation procedures might also influence the results.

As reported by others, we could confirm that responders had a significantly better survival than non-responders [3, 12, 13]. Similarly to the reports by Young *et al.* [3] and Edmonson *et al.* [10], we found a far better survival in patients having minimal residual disease than patients with a bulky residue.

In stage II_B patients treated with chemotherapy irradiation had no beneficial impact on survival. However, the number of patients is small and no final conclusion concerning the use of radiation therapy in this stage can be made from the present study.

With respect to future cytostatic treatment of ovarian cancer, it is noteworthy that Vogl *et al.* in an early phase II study have shown an extremely high response rate for cisplatin-containing regimens [18]. Most ongoing studies today, including our own, are now focusing on combination chemotherapy containing cisplatin. In randomized studies the median survival rates are stated to be approximately 24 months, with a response rate of 50-80% [19]. These encouraging results may indicate that cisplatin regimens may lead to additional therapeutic improvement for advanced carcinoma of the ovary.

Acknowledgements—We thank Miss Charlotte Meldal for secretarial assistance in the preparation of this manuscript and Dr Kell Østerlind for statistical assistance.

REFERENCES

1. Tobias JS, Griffiths CT. Management of ovarian carcinoma. *N Engl J Med* 1976, **294**, 818-823.
2. Katz ME, Schwartz PE, Kapp DS, Luikart S. Epithelial carcinoma of the ovary: current strategies. *Ann Intern Med* 1981, **95**, 98-111.

3. Young RC, Chabner BA, Hubbard SP *et al.* Advanced ovarian adenocarcinoma. A prospective clinical trial of melphalan (L-PAM) versus combination chemotherapy. *N Engl J Med* 1978, **299,** 1261-1266.
4. Pedersen-Bjergaard J, Nissen NI, Sørensen HM *et al.* Acute non-lymphocytic leukemia in patients with ovarian carcinoma following long-term treatment with treosulfan (=dihydroxybusulfan). *Cancer* 1980, **45,** 19-29.
5. Serov SF, Scully RE, Solvin LH. *International Histological Classification of Tumors, No. 9. Histological Typing of Ovarian Tumors.* Geneva, WHO, 1973.
6. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO, 1979.
7. Aabo K, Pedersen AG, Hald I, Dombernowsky P. High-dose medroxyprogesterone acetate (MPA) in advanced chemotherapy-resistant ovarian carcinoma: a phase II study. *Cancer Treat Rep* 1982, **66,** 407-408.
8. Maskens AP, Armand J-P, Lacave AJ, De Jager RL, Hansen HH, Wolff J-PM. Phase II clinical trial of VP-16-213 in ovarian cancer. *Cancer Treat Rep* 1981, **65,** 329-330.
9. Dombernowsky P, Siegenthaler P, Somers R, Hansen HH. Phase II trial of amsacrine (*m*-AMSA) in advanced ovarian carcinoma. *Eur J Cancer Clin Oncol* 1982, **18,** 71-74.
10. Edmonson JH, Fleming TR, Decker DG *et al.* Different chemotherapeutic sensitivities and host factors affecting prognosis in advanced ovarian carcinoma versus minimal residual disease. *Cancer Treat Rep* 1979, **63,** 241-247.
11. Bolis G, Bortolozzi G, Carinelli G *et al.* Low-dose cyclophosphamide versus adriamycin plus cyclophosphamide in advanced ovarian cancer. *Cancer Chemother Pharmacol* 1980, **4,** 129-132.
12. Omura GA, Morrow CP, Blessing JA *et al.* A randomized comparison of melphalan versus melphalan plus hexamethylmelamine versus adriamycin plus cyclophosphamide in ovarian carcinoma. *Cancer* 1983, **51,** 783-789.
13. Park RC, Blom J, DiSaria PJ, Lagasse LD, Blessing JA. Treatment of women with disseminated or recurrent advanced ovarian cancer with melphalan alone, in combination with 5-flourouracil and dactinomycin or with the combination of cytoxan, 5-flourouracil and dactinomycin. *Cancer* 1980, **45,** 2529-2542.
14. Carmo-Pereira J, Costa FO, Henriques E, Ricardo JA. Advanced ovarian carcinoma: a prospective and randomized clinical trial of cyclophosphamide versus combination cytotoxic chemotherapy (hexa-CAF). *Cancer* 1981, **48,** 1947-1951.
15. Carmo-Pereira J, Costa FO, Henriques E. *Cis*-platinum, adriamycin and hexamethylmelamine versus cyclophosphamide in advanced ovarian carcinoma. *Cancer Chemother Pharmacol* 1983, **10,** 100-103.
16. Bruckner HW, Pagano M, Falkson G *et al.* Controlled prospective trial of combination chemotherapy with cyclophosphamide, adriamycin and 5-flourouracil for the treatment of advanced ovarian cancer: a preliminary report. *Cancer Treat Rep* 1979, **63,** 297-299.
17. Barlow JJ, Piver MS. Single agent vs combination chemotherapy in the treatment of ovarian cancer. *Obstet Gynecol* 1977, **49,** 609-611.
18. Vogl SE, Berenzweig M, Kaplan BH, Moukhtar M, Bulkin W. The CHAD and HAD regimens in advanced ovarian cancer: combination chemotherapy including cyclophosphamide, hexamethylmelamine, adriamycin and *cis*-dichlorodiammine-platinum (II). *Cancer Treat Rep* 1979, **63,** 311-317.
19. Cohen CJ, Goldberg JD, Holland JF *et al.* Improved therapy with cis-platin 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.