Cancer Chemother. Pharmacol. 4, 129–132 (1980)

Cancer Chemotherapy and Pharmacology

Short Communication

Low-dose Cyclophosphamide Versus Adriamycin plus Cyclophosphamide in Advanced Ovarian Cancer

A Randomized Clinical Study

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Summary. *After intensive staging 74 ovarian cancer patients were randomized to two arms balanced for stage and post-surgery residual tumor. The two regimens were CTX 100 mg/day continuously and ADM 50 mg/m² IV every 4 weeks plus CTX 100 mg/day. The response rates were respectively 42% and 52%. Median survival times were 13 and 14 months. The incidence of side effects was significantly higher in the combination-treatment arm. No other statistical differences were found.*

Introduction

Alkylating agents are the drugs used most extensively in advanced ovarian cancer (FIGO Stages III and IV). They are easy to use, adequately tolerated, and at present induce responses in 30%–60% of patients, with no significant difference between the various drugs. The regimens used are also similar: low daily oral doses [9], intermittent IV [15], intermittent high IV doses [14]. As an alternative to alkylating agents, adriamycin was studied in a limited group of patients, and compared favourably with melphalan [4]. The association of adriamycin and cyclophosphamide was also somewhat more effective than monochemotherapy in ovarian cancer [11]. Edmonson et al. [5] reported the superiority of cyclophosphamide plus adriamycin over cyclophosphamide alone in minimal residual ovarian cancer, but did not find any difference in more advanced Stage III and IV cases.

The aim of the present study was therefore to obtain additional data from a controlled trial of this combination, which, despite some conflicting results, appears to be promising.

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Caselist and Methodology

Seventy-four patients with epithelial ovarian cancer, aged between 19 and 80 years and with a life expectancy of more than 3 months, who had never been treated before by radiation or chemotherapy and in whom bone marrow and hepatic and renal function were normal, were admitted to protocol OC/175, UICC N. 76014 between November 1975 and December 1977.

Surgery was performed according to the bulk of the disease: simple laparotomy excision of masses, or complete pelvic surgery (total abdominal hysterectomy + bilateral salpingoophorectomy and omentectomy, TAH BSOO). Cytological examination of ascites or peritoneal washing, lymphangiogram, and lymph node excision or biopsy were performed when indicated.

After histological characterization, patients were stratified according to Stage (III and IV FIGO) and residual tumor after surgery (III late > 2 cm, early ≤ 2 cm and no residual).

Intensive anatomical X-ray and surgical staging was performed in all patients operated on in our Department or referred from outside (laparoscopic restaging and roentgenographic studies within 40 days of primary surgery).

Patients were randomized after eligibility and stage had been checked 10 days after surgery. Histology and grading were not among the criteria considered for randomization. Table 1 reports the details of the caselist.

The chemotherapy program comprised the two following regimens: cyclophosphamide (CTX) 100 mg/day PO, continuously or cyclophosphamide 100 mg/day PO, continuously, plus adriamycin (ADM) 50 mg/m² by IV bolus every 4 weeks. ADM was stopped at 450 mg/m² and treatment was maintained with CTX alone on a continuous low-dose regimen.

Treatment was continued for at least 3 months, in each case for as long as the patient remained in remission or until progression occurred, at which stage patients were withdrawn from this protocol. During treatment, WBC, platelets, Hb, hematocrit and liver function were monitored every 2 weeks, and an ECG was performed monthly. At the following threshold values treatment was stopped until normalization: WBC $\leq 2000/\mu l$ platelets $\leq 75{,}000/\mu l$, bilirubin ≥ 3 mg%, SGPT > 50 U. At the second toxic event patients were given a reduced dosage consisting of 14 doses of 100 mg CTX day and one of 25 mg ADM/m² every 4 weeks.

Follow-up consisted of a thorough physical and pelvic examination every 4 weeks with X-rays at least every 3 months.

Response was assessed from roentgenographic studies and laparoscopy with peritoneal cytology in responders after 8 months of

0344-5704/80/0004/0129/$ 01.00

Table 1. Characteristics of patients

	CTX	CTX + ADM
No. of patients	37	37
No residual tumor	4	4
Residual tumor	33	33
Residues < 2 cm	7	7
Residues > 2 cm	26	26
FIGO stage		
III	30	30
IV	3	3
Histological type		
Serous	31	29
Mucinous	–	3
Endometrioid	2	1
Histological grade (Broders)		
1–2	9	13
3–4	24	20
Ascites	18	18
Age	56 (18–80)	53 (31–74)

CTX or after the maximal doses of ADM were reached. Complete response (CR) was defined as the complete disappearance of tumor residues for at least 3 months; partial response (PR), as the reduction by more than 50% of at least one tumoral mass for the same period of time; no change (NC) as either reduction or increase of one tumoral mass by less than 50%. Progression (PG) was an increase by more than 50% or the appearance of a new tumoral mass.

All patients who were clinically free of disease after 24 months of chemotherapy underwent a second-look laparotomy following negative peritoneoscopy. Early and no-residual Stage III patients were submitted to second-look laparatomy after two or more negative peritoneoscopies. Patients with negative second-look stopped chemotherapy.

Response rates and toxic effects were compared by the X^2-test. Median survival was calculated by Kaplan-Meyer's method.

Results

Six out of eight patients with no residual tumor are alive and free of disease at a follow-up time of 13–36 months. Two died with progression after 32 and 29 months of treatment with CTX and CTX + ADM, respectively. Tables 2 and 3 show the survival and response rates of patients with residual disease according to the stratification and to the type of treatment. No statistical difference was found between the results of chemotherapy with CTX alone and in combination with ADM; the response rate with the single agent was 42% (12% CR) and with the combination, 52% (18% CR), confidence limits at $P = 0.05$ ranging from 26%–61% and 34%–69%.

The type of surgery performed does not appear to be related to the response to chemotherapy (Table 4). Nine of 14 and 9 of 20 Grade 1–2 patients and 7 of 18 and 11 of 16 Grade 3–4 patients responded, respectively, to CTX and CTX + ADM; the differences were not statistically significant. The overall response rate was 76% in Grade 1–2 patients and 40% in Grade 3–4 patients; this difference was at the limits of statistical significance. Lymph node involvement, checked lymphographically, did not appear to be in any way related to response rate. The same can be stated for the presence of ascites.

Clinical evaluation of response was compared with the laparoscopic evaluation in 23 responders. CR was confirmed in three of nine patients with masses > 2 cm and in seven of eight patients with masses < 2 cm. PR was confirmed in six out of six. Of seventeen clinically evaluated CR, seven were not confirmed and after laparoscopy these were reclassed as three PRs, three NCs, and one PG. To date laparotomy has been carried out only in two complete responders after 24 months of chemotherapy.

Toxicity induced by the two regimens is summarized in Table 5. Gastric toxicity and alopecia were significantly more frequent with the combination, which caused a higher incidence for each parameter evaluated. Temporary withdrawal of therapy and dose reduction were consequently necessary more frequently in this group ($P < 0.001$ and < 0.025, respectively).

Discussion

The results of the present study do not indicate any superiority of the combination of CTX + ADM over CTX alone in the treatment of advanced ovarian cancer. The response rate we observed is perfectly consistent with previous reports [1, 5, 8], but is not in agreement with the hopeful communication by Turbow et al. [12], reporting a response rate of 72% (54% CR). However, this study was not in fact comparable with ours, because an unspecified number of cases were previously irradiated Stage I and II patients and, furthermore, such a high percentage of CR was presumably affected by the limitation of only clinical evaluation. We noted in our study that only ten of the seventeen CR recorded on clinical evaluation were confirmed laparoscopically.

The superiority of ADM + CTX over CTX alone in early residual disease reported by Edmonson et al. [5] is not confirmed in our study; we observed, in fact, a very similar response rate with both regimens; the limited number of early and nonresidual patients could be the reason for this discrepancy.

In terms of toxicity our data consistently indicate greater toxicity with the association of ADM and CTX, though the levels reached were never life-threatening.

Table 2. Median survival and range (months) in 66 patients with residual tumor

Response	> 2 cm		< 2 cm	
	CTX	CTX + ADM	CTX	CTX + ADM
Complete	–	17+ (17+; 33+)	17+ (12+; 31+)	14+ (11+; 32+)
Partial	10+ (4; 31+)	13 (9; 19)	–	–
No change	10+ (9+; 30+)	9	–	–
Progression	8 (3; 14)	5.5 (2; 10+)	9 (9; 10+)	11+ (9; 19)
Total	10 (3; 31+)	10 (2; 33+)	12+ (9; 31)	11+ (9; 32+)

Table 3. Response of patients with residual tumor

Response	> 2 cm						< 2 cm					
	CTX			CTX + ADM			CTX			CTX + ADM		
	Patients		Months[a]	Patients		Months[a]	Patients		Months[a]	Patients		Months[a]
	No.	%[b]		No.	%[b]		No.	%[b]		No.	%[b]	
Complete	0	0–13		3	2–30	15+ (11; 33+)	4	18–90	17 (12+; 31+)	3	10–82	14+ (11+; 32+)
Partial	10	20–59	7 (4; 13+)	11	23–63	7 (5; 10)	0					
No change	5	7–39		2	1–25		0					
Progression	11	23–63		10	20–59		3	10–82		4	18–90	
n	26			26			7			7		
CR + PR	10	20–59		14	33–73		4	18–90		3	10–82	

[a] Median and (range)
[b] Confidence limits of the percentage ($P = 0.05$)

Table 4. Response of patients in postsurgery Stage III late, according to surgery performed

	PR + CR		Total
	CTX	CTX + ADM	
Simple laparotomy with biopsies	6/14 (43%)	5/10 (50%)	11/24 (46%)
Partial exeresis (excision of masses)	4/8 (50%)	5/11 (45%)	9/19 (47%)
Complete pelvic surgery	0/4	4/5 (80%)	4/9 (44%)

Table 5. Patients suffering toxicity

	CTX (37 patients)	CTX + ADM (37 patients)
Temporary withdrawal of therapy	3	19[b]
Dose reduction	1	7[a]
WBC nadir 2000	3	7
Platelets nadir 100,000	3	5
Hemoglobin 12 g/100 ml	8	14
Nausea	18	37[b]
Vomiting	–	30[b]
Alopecia	22	36[b]
Hemorrhagic cystitis	–	2
Herpes	1	2

[a] $P < 0.025$; [b] $P < 0.001$ (χ^2-test)

When tumor residues are > 2 cm, excision of masses does not influence the response rate, as already reported [7].

Broders' histological grading indicated a better response, though not statistically significant, in Grade 1–2 than in Grade 3–4 patients. This fact is in agreement with reports of the prognostic importance of grading being less in Stage III late and Stage IV [3]. Lymphangiographic examination gave no prognostic information and is discussed in detail elsewhere [10]. The presence of ascites also appeared to be irrelevant to the prognosis.

As a general conclusion, it seems that ADM associated with low-dose CTX does not benefit patients in our experimental conditions. This does not exclude the possibility that this combination could give better results when CTX is administered at high intermittent doses simultaneously with ADM. So far there is only a limited number of studies showing the superiority of polychemotherapy, though a trend emerges in Young's study, which showed a promising improvement with a regimen of four drugs such as Hexa-CAF [16].

Regimens including ADM in association with CTX and *cis*-dichlorodiaminoplatinum [2, 6] and, more recently, including hexamethylmelamine in addition [13] appear to be promising; though the results of the present study do not statistically support the superiority of polychemotherapy in the conditions tested we think this may be the path to follow to improve the management of ovarian cancer.

References

1. Alberts DS, Moon TE, Stephens RA, Wilson H, Oishi N, Hilgers RD, O'Toole R, Thigpen JT (1979) Randomized study of chemoimmunotherapy for advanced ovarian carcinoma: A preliminary report of a Southwest Oncology Group Study. Cancer Treat Rep 63:325
2. Bruckner HW, Wallach RC, Kabakow B, Greenspan EM, Gusberg SB, Holland JF (1978) *cis*-Platinum (DDP) for combination chemotherapy of ovarian carcinoma: Improved response rates and survival. Proc Am Assoc Cancer Res 19:373
3. Decker DG, Malkasian GD, Taylor WF (1975) Prognostic importance of histologic grading in ovarian carcinoma. Natl Cancer Inst Monogr 42:9
4. De Palo GM, De Lena M, Di Re F, Luciani L, Valagussa D, Bonadonna G (1975) Melphalan versus adriamycin in the treatment of advanced carcinoma of the ovary. Surg Gynecol Obstet 141:899
5. Edmonson JH, Fleming TR, Decker DG, Malkasian GD, Jorgensen EO, Jefferies JA, Webb MJ, Kvols LK (1979) Different chemotherapeutic sensitivities and host factors affecting prognosis in advanced ovarian carcinoma versus minimal residual disease. Cancer Treat Rep 63:241
6. Ehrlich CE, Einhorn LH, Morgan JL (1978) Combination chemotherapy of ovarian carcinoma with *cis*-diamminedichloroplatinum (CDDP), adriamycin (ADR) and cytoxan (CTX). Proc Am Assoc Cancer Res 19:379
7. Griffiths CT (1975) Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 42:101
8. Lloyd RE, Jones SE, Salmon SE, Durie BGM, McMahon LJ (1976) Combination chemotherapy with adriamycin (NSC-123127) and cyclophosphamide (NSC-26271) for solid tumors: A phase II trial. Cancer Treat Rep 60:77
9. Mangioni C, Bolis G, Natale N, Morasca L (1976) Continuous low-dose cyclophosphamide (NSC-26271) therapy in advanced ovarian cancer. Eur J Cancer 12:353
10. Musumeci R, Banfi A, Bolis G, Candiani GB, De Palo G, Di Re F, Luciani L, Lattuada A, Mangioni C, Mattioli G, Natale N (1977) Lymphangiography in patients with ovarian epithelial cancer. Cancer 40:1444
11. Parker LM, Lokich JJ, Griffiths CT, Frei E III (1975) Adriamycin-cyclophosphamide therapy in ovarian cancer. Proc Am Assoc Cancer Res 16:263
12. Turbow MM, Fuks Z, Glatstein E (1978) Chemotherapy of ovarian carcinoma: Randomization between melphalan and adriamycin-cyclophosphamide. Proc Am Assoc Cancer Res 19:394
13. Vogl SE, Berenzweig M, Kaplan BH, Moukhtar M, Bulkin W (1979) The CHAD and HAD regimens in advanced ovarian cancer: Combination chemotherapy including cyclophosphamide, hexamethylmelamine, adriamycin and *cis*-dichlorodiammine platinum (II). Cancer Treat Rep 63:311
14. Young RC, Canellos GP, Chabner BA, Schein FS, Hubbard SP, De Vita VT (1974a) Chemotherapy of advanced ovarian carcinoma: A prospective randomized comparison of phenylalanine mustard and high-dose cyclophosphamide. Gynecol Oncol 2:489
15. Young RC, Hubbard SP, De Vita VT (1974b) The chemotherapy of ovarian cancer. Cancer Treat Rev 1:99
16. Young RC, Chabner BA, Hubbard SP, Fisher RI, Bender RA, Anderson T, Simon RM, Canellos GP, De Vita VT (1978) Advanced ovarian adenocarcinoma. A prospective clinical trial of melphalan (L-PAM) versus combination chemotherapy. N Engl J Med 299:1261

Received May 10, 1979/Accepted January 11, 1980