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Prospective Study with HEXA-CAF Combination in Ovarian Carcinoma

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Summary. *The value of combination chemotherapy with HEXA-CAF was analyzed in 31 patients with histologically documented epithelial ovarian cancer in advanced stages (minimal or gross disease). No patient had been previously treated with chemotherapy. Peritoneoscopy with diaphragmatic inspection, peritoneal cytology, lymphography, and chest X-ray were routinely used in staging and restaging the patients. Complete (CR) plus partial (PR) responses were obtained in 13/31 fully restaged patients (41.9%). CR was recorded in seven patients (22.5%) and PR in six patients (19.3%). Remission duration was significantly longer in patients who achieved CR (20 months) than in those who attained PR (9.5 months) ($P < 0.01$). In all treated patients the median duration of survival was 16.5 months. Survival was significantly longer in patients with CR than in patients who did not achieve CR ($P < 0.05$). Nevertheless, considering the rate of CR in patients with gross disease (20.6%), HEXA-CAF combination seems a useful but not yet a hopeful treatment for patients with advanced ovarian carcinoma.*

Introduction

Ovarian carcinoma is one of the most responsive solid tumors to chemotherapy, and, in fact, impressive remissions have been seen in clinical practice. Melphalan (L-PAM), cyclophosphamide (CTX), adriamycin (ADM), hexamethylmelamine (HMM) and *cis*-diamminedichloroplatinum (CDDP) are the most effective single drugs and can produce complete or partial remission in about 40% of patients [1, 4, 5, 11, 16, 17, 19]. However, the frequency of complete remission was no greater than 15%–20% and the median duration of survival in responder patients was not superior to 20 months. The disappointing results obtained with single-agent chemotherapy has stimulated a new interest in multiple-drug chemotherapy, which has given excellent results in the treatment of other tumor types.

Combination chemotherapy known as HEXA-CAF (hexamethylmelamine-cyclophosphamide-amethopterin and fluorouracil), when used in the series reported by National Cancer Institute of Bethesda [21], produced complete or partial response in 75% of patients fully restaged, as against 54% of patients treated with L-PAM. Complete response was obtained in 33%, with a median duration superior to 30 months, vs 16% with a median duration of 25 months in patients treated with L-PAM. In all treated patients the median duration of survival (29 months) was greater than that reported for patients responsive to single-agent chemotherapy.

In this paper we report the results obtained with this combination at the Istituto Nazionale Tumori of Milan.

Materials and Methods

Criteria for Inclusion in the Study

From July 1976 to June 1979, 33 patients with histologically documented epithelial ovarian cancer in advanced stages (minimal or gross disease) and previously untreated with chemotherapy entered the study. Patients with an estimated life expectancy of less than 2 months and patients with germinal or malignant stromal ovarian tumors or suspicion of a tumor at another primary site were not admitted to the study.

Staging Procedures

Two groups of patients were treated. The first, and predominant, group comprised those (20 patients) in whom the initial operation

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was performed in other hospitals. The second group comprised those (13 patients) treated from the beginning in our Institute. In the first group all the medical records and slides were reviewed.

The work-up was as follows: peritoneoscopy with diaphragmatic inspection and biopsies, peritoneal cytology (ascites or peritoneal washing, or both) lymphography, chest roentgenogram, in addition to physical and pelvic examination. Double-contrast enema and intravenous urography were performed in some patients. Pretreatment observations included the following chemistry tests: alkaline phosphatase, serum bilirubin, SGOT, SGPT, serum electrolytes, blood urea nitrogen, serum creatinine, uric acid, and total proteins. Chemistry tests were repeated every two cycles and a hemogram with differential and platelet counts before every cycle. In patients operated on in our Institute surgical staging was performed [6]. The results of this staging were used to determine the patient's final Figo (1975) stage.

Drug Regimens and Assessment of Response

Patients were treated with a four-drug combination employed as follows: 5-fluorouracil at 600 mg/m^2 and methotrexate at 40 mg/m^2 given IV on days 1 and 8; cyclophoshamide and hexamethylmelamine given at 100 mg/m^2 PO daily for the first 14 days of the cycle. From days 15 through 28, no therapy was given. The above regimen constitutes one cycle.

A dosage reduction schedule was used if myelosuppression was present. The dosage adjustment was performed on the basis of the grade of hematologic toxicity, categorized according to the leukocyte and platelet count carried out on the same day as drug administration. If no toxicity was evident (leukocyte count $\geq$ 4,000 and platelet count $\geq$ 130,000/mm^3) full drug doses were administered. For grade 1 toxicity (leukocyte count equal to 3,999–2,500/mm^3 or platelet count equal to 129,000–80,000/mm^3 or both) 50% of the calculated dose was given. In the presence of grade 2 toxicity (leukocyte count $<$ 2,500 or platelet count $<$ 80,000/mm^3 or both) no drug was administered until at least grade 1 toxicity was reached.

The patients received intermittent therapy for 6 months if response was evident. Every month the patients were subjected to clinical and gynecologic examination. In patients in whom clinical progression during treatment was evident and confirmed by radiologic and/or peritoneoscopic studies, therapy with adriamycin and *cis*-diamminedichloroplatinum, both IV at the dose of 50 mg/m^2, was administered every 21 days. After six cycles of therapy all patients with response or no change underwent restaging with roentgenographic studies and peritoneoscopy including peritoneal cytology. Patients whose peritoneoscopy was negative underwent second-look laparotomy. Patients with residual disease after restaging were treated for an additional six cycles of therapy before restaging of the disease was repeated. Patients with complete regression after second-look laparotomy were treated with two additional cycles of therapy.

Response Criteria

Complete remission (CR) was defined as disappearance of all evidence of disease by clinical, radiologic and peritoneoscopic restaging. Partial remission (PR) was defined as at least 50% reduction of measurable disease after complete restaging. In the presence of residual disease at peritoneoscopic restaging the remission was calculated as partial. Stable disease (SD) was defined as disease not meeting either of the above two criteria. Progressive disease (PD) was defined as an increase in size of any lesion by more than 25% or the appearance of any new lesion. The duration of response was calculated from the onset of chemotherapy. Survival was defined as the observed length of life from entry in the study to death or, for living patients, the date of last contact.

Patient Selection

Thirty-three patients entered the study and, two patients having been lost to follow-up before completion of one treatment cycle, 31 are considered evaluable for response.

The characteristics of the patients are reported in Table 1. The mean age was 53.7 years (range 33–72); the FIGO classification

Table 1. Characteristics of 31 evaluable patients

Age	
$<$ 50 years	10
$\geq$ 50 years	21
Histologic type	
Serous	20
Mucinous	3
Endometrioid	2
Clear cell	1
Unclassified	5
Histologic grade	
Grade I	7
Grade II	15
Grade III	4
Grade not determined	5
Time from diagnosis to entry on study	
$\leq$ 1 month	14
1–3 months	9
4–12 months	2
$>$ 12 months	6
Surgery	
Biopsy only[a]	18
Excision of masses	2
BSO + TAH + omentectomy	11
Stage	
III	16
IV	9
Recurrence	6
Disease	
Minimal	2
Intraperitoneal and pelvic $>$ 2 cm	13
Intraperitoneal and pelvic + retroperitoneal	5
Extraperitoneal (liver and/or extraabdominal) $\pm$ intraperitoneal $\pm$ retroperitoneal	11
Prior radiotherapy	
No	30
Yes	1

[a] Laparoscopy or exploratory laparotomy; BSO, bilateral salpingo-oophorectomy; TAH, total abdominal hysterectomy

showed that 16 were in stage III and nine in stage IV. Six patients were recurrences.

Biopsies during laparotomy or laparoscopy were carried out in 18 patients, while 11 patients had bilateral ovarosalpingectomy plus total abdominal hysterectomy ± omentectomy; in two patients reductive surgery was performed. The extent of residual disease after surgery shows that 13 patients had intraperitoneal and pelvic disease greater than 2 cm in diameter, five patients had intraperitoneal and pelvic plus retroperitoneal disease, and 11 patients had liver and/or extra-abdominal ± intraperitoneal ± retroperitoneal disease. Two patients only had minimal residual disease defined as positive peritoneal cytology (one patient) and diaphragmatic or peritoneal disease less than 2 cm in diameter (one patient) or both. One patient was pretreated with radiotherapy. All patients were subjected to complete restaging and five to second-look laparotomy.

Pathology

The histologic type of malignant 'epithelial' ovarian tumors was defined according to the World Health Organization's criteria [15]. The majority of patients had a serous cystadenocarcinoma. The number of unclassified carcinomas was due to the type of material that we examined. In fact, in five cases the histologic diagnosis referred to the peritoneoscopic biopsies. The degree of malignancy was classified, for all the histotypes, as I, II, or III, respectively, for well-differentiated, moderately differentiated, and undifferentiated forms. The criteria used to define the grading were similar to those proposed by Russell [13, 14], and they were based on the analysis of the histologic structure, the degree of cellular anaplasia, and the mitotic index [6]. According to these criteria seven patients had grade I disease, 15 grade II, and four grade III.

Results

Table 2 shows the type of response after HEXA-CAF combination treatment. CR plus PR was observed in 13/31 patients who were fully restaged (41.9%). CR occurred in seven patients (22.5%), one with minimal residual and six with gross disease (Table 3). Four patients were submitted to radical surgery after complete clinical, peritoneoscopic, cytologic, and radiologic remission. In three of these patients residual disease was pathologically evident (microscopic disease in one ovary in two patients at peritoneal and retroperitoneal initial stage III and at peritoneal stage III, respectively; microscopic disease in bilateral ovaries, omentum and left para-aortic node in one patient at initial stage IV for distant metastases), while in one patient at stage III for peritoneal and retroperitoneal disease, no residual disease was evident. Median duration of CR was 20 months. All four patients who have relapsed so far had gross disease. Three patients with CR are still living in remission (15, 26, and 39 months from start of therapy), and two of these had radical surgery after chemotherapy.

PR was observed in six patients (19.3%), with a median duration of response of 9.5 months; one of them, with pelvic remission greater than 50%, was submitted to second-look laparotomy with reductive surgery. Seven patients (22.5%) had stable disease with a median duration of 10 months, while in 11 patients (35.4%) there was progression of disease during treatment. Remission duration was significantly longer in patients who achieved CR (35.7% are still in remission after 25 months) than in those who obtained a PR ($P < 0.01$) (Fig. 1). All patients who achieved PR showed progression within 12 months from the start of treatment. In all treated patients the median duration of survival was 16.5 months; this median duration of survival for patients with CR has not yet been reached, but it probably will exceed 21 months. After 27 months from starting treatment (Fig. 2) only 7.9% of patients not achieving CR are alive, as against 51.4% of CR patients ($P < 0.05$) [12].

The influence of histologic grading could not be evaluated because of the small number of cases in each subcategory. Nevertheless, whereas the histologic grade, determined in 26 patients from the

Table 2. Response to HEXA-CAF (clinical, radiological and peritoneoscopic evaluation)

Type of response	No. of patients		Median duration of response (months)
Complete response	7 (22.5%)	13/31 (41.9%)	20[a]
Partial response	6 (19.3%)		9.5
Stable disease	7		10
Progressive disease	11		

[a] Four patients with radical surgery post-chemotherapy

Table 3. Response to HEXA-CAF according to extent of disease

Extent of disease	No. of cases	CR	PR	SD	PD
Minimal[a]	2	1	–	1	–
Intraperitoneal and pelvic > 2 cm	13	2	2	6	3
Intraperitoneal and pelvic + retroperitoneal	5	2	2	–	1
Extraperitoneal (liver parenchyma and/or extra-abdominal) ± intraperitoneal ± retroperitoneal	11	2	2	–	7
Total	31	7	6	7	11

[a] See text

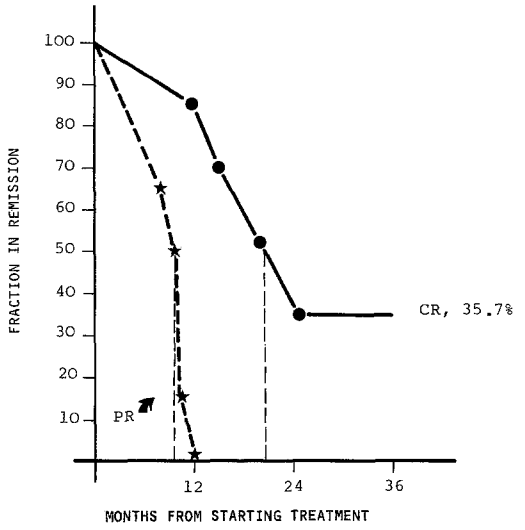

Fig. 1. Duration of remission. CR vs PR: $P < 0.01$

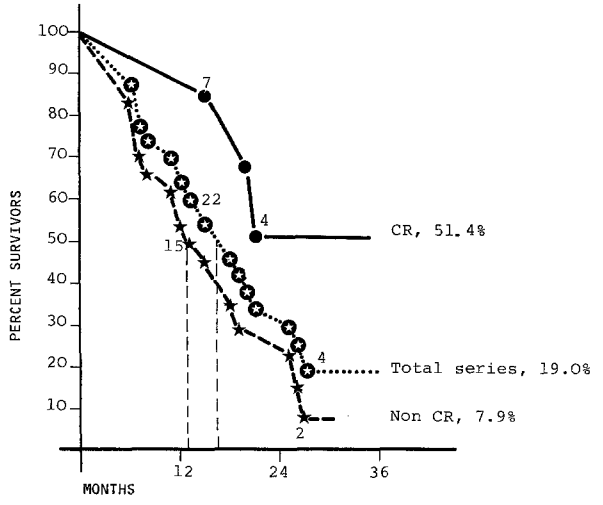

Fig. 2. Duration of survival. CR vs Non CR: $P < 0.05$

primary tumor, did not correlate with response to therapy, it seemed to exert an influence on prognosis. Four of seven patients with well-differentiated (grade I) carcinoma are still alive (17, 24, 25, and and 31 months from start of therapy), compared with three of 15 patients with moderately differentiated (grade II) (12, 30, 39 months) and none of four patients with undifferentiated (grade III) carcinoma.

Toxicity

Side-effects were present in all the 31 patients evaluable for therapy (Table 4). Leukopenia was evident in 93.5% and thrombocytopenia in 48.3% of the patients, four of whom had a severe grade of myelosuppression. Anemia, defined as loss of a minimum of 2 g hemoglobin in the absence of any gross or microscopic hematic leak, was evident in 54.8% of patients. Other toxic effects were evident in a large number of patients, but did not affect the therapy. Because of hematologic toxicity, the doses were modified. The percentage of the total projected dose administered gradually decreased during the six cycles of treatment from 90% at cycle 1 to 79% at cycle 3 and 67% at cycle 6.

Table 4. Side-effects in 31 evaluable patients

Side-effects	No. of cases
Total patients with side-effects	31
Leukopenia	29 (93.5%)
Grade I (3,999–2,500)	16
Grade II (< 2,500)	13
Thrombocytopenia	15 (48.3%)
Grade I (129,000–80,000)	11
Grade II (< 80,000)	3
Grade III (< 50,000)	1
Anemia (– 2 g)	17 (54.8%)
Loss of hair	21
Vomiting	19
Diarrhea	3
Stomatitis	3
Cystitis	13
Conjunctivitis	11

Discussion

The HEXA-CAF combination demonstrated some activity in the treatment of advanced ovarian carcinoma. In fact, the CR plus PR rate measured by accurate restaging was 42%, and the CR rate was 22.5%, with a median duration of remission of 20 months. Comparison of response duration demonstrated statistically significant differences ($P < 0.01$) between patients who achieved CR and those who attained only a PR, and the patients with CR had a significantly higher survival rate ($P < 0.05$) than the patients in other categories.

Cumulatively considered, these results are largely inferior to those reported by Young et al. [21] and by Neut et al. [9], but these differences are more apparent than true. In fact, in spite of the lower dose of CTX and HMM, the major reduction of doses of the four drugs, and the presence of one patient pretreated with radiotherapy in our series, CR was obtained in one of two patients with minimal residual disease and in six of 29 patients with gross disease (20.6%). In the NCI series, CR was obtained in eight of eight patients with disease less than 2 cm in diameter (and three of these had microscopic disease)

and in five of the remaining 32 patients with disease greater than 2 cm in diameter (15.6%).

The better results in the NCI series are based on the large number of partial responses, which in our study were evaluated after complete restaging, while the different survival rate depends on the comparatively large number of patients with residual tumors measuring less than 2 cm in diameter. Therefore our findings are similar to those reported by Young et al. [21]. However, we feel that ours are not satisfactory, because the incidence of CR in patients with gross disease is still low, especially when compared with early findings achieved with other combination chemotherapies [2, 3, 7, 8, 10, 18, 20].

In conclusion, HEXA-CAF combination is a useful but not yet a hopeful treatment for patients with advanced ovarian carcinoma.

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