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Hexamethylmelamine, adriamycin, and cyclophosphamide (HAC) versus *cis*-dichlorodiamineplatinum, adriamycin, and cyclophosphamide (PAC) in advanced ovarian cancer: A randomized clinical trial*

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Summary. *After stratification according to diameter of the largest residual tumor, 120 previously untreated ovarian cancer patients were randomized to receive adriamycin and cyclophosphamide in combination with hexamethylmelamine (HAC) or cis-dichlorodiamineplatinum (PAC). The surgical response rates were 66% to HAC and 70% to PAC, with median times to progression of 14 and 22 months and median survival times of 23 and 24 months, respectively. In patients with residual tumor > 2 cm the surgical response rates to HAC and PAC were 56% and 63%, with complete response rates of 13% and 21%, respectively. In two of five complete responders to HAC there has still been no progression at 38 and 48 months, with a median response duration of 25 months. Only one of the nine complete responders to PAC has relapsed, at 33 months, while in the eight others response is maintained at follow-up times of 35–64 months. Myelosuppression was generally mild and similar in the two arms. No significant nonhematological toxicity was reported. It is concluded that at a median follow-up time of 36 months HAC is as effective as PAC in terms of response, duration of remission, and survival in previously untreated advanced ovarian cancer.*

Introduction

Though epithelial ovarian cancer is a human malignancy that is sensitive to alkylating agents, the results with these compounds in advanced disease have so far been poor in terms of complete response rate, and the reported survival at 5 years is only 5%–10% [24]. The promising results achieved with combination chemotherapy in other human tumors and the availability of new drugs with some activity in ovarian cancer, other than traditional alkylating agents, have prompted many tests of multidrug regimens in this neoplasia. In 1972 NCI started a randomized clinical trial comparing melphalan alone with the combination of hexamethylmelamine, cyclophosphamide, 5-fluorouracil, and methotrexate (Hexa-CAF). This study demonstrated the superiority of multidrug therapy over monochemotherapy in ovarian cancer for the first time and provided encouragement for other trials using combination chemotherapy, including drugs with proven activity in this disease [25].

Apart from hexamethylmelamine, believed to be the agent responsible for the success reported with Hexa-CAF, the other new compound with interesting potential appeared to be *cis*-dichlorodiamineplatinum, which had proved active as a single agent in refractory ovarian cancer [22] and had shown synergistic activity with adriamycin [3] and cyclophosphamide in rodent tumors [23].

With the aim of finding better multidrug regimens with high efficacy and tolerable toxicity, in 1978 we decided to test the activity in stage III–IV ovarian cancer of adriamycin + cyclophosphamide, since this association had yielded promising preliminary results [12], in combination with *cis*-dichlorodiamineplatinum or hexamethylmelamine. This paper reports the results of this study up to September 1983.

Patients and methods

Patients were required to have a histological diagnosis of epithelial ovarian cancer in stage III or IV (FIGO classification); estimated survival of at least 3 months; age less than 70 years; performance status greater than 70 on the Karnofsky scale; leukocyte and platelet counts greater than 3,000 cells/μl and 100,000/μl; serum creatinine less than 1.2 mg/100 ml; and total bilirubin less than 1.5 mg/100 ml. Only patients who had not previously received chemotherapy or radiotherapy were eligible for this trial. Histological typing and grading were performed by the staff of the Department of Pathology, 1st Clinic of Obstetrics and Gynaecology, University of Milan. The pattern grading system was used [5]. Informed consent was obtained from each patient.

On admission, patients had a physical and pelvic examination. Laboratory evaluation consisted in complete blood count, BUN, creatinine, creatinine clearance, serum electrolytes, liver function tests. X-Ray studies included chest roentgenogram, intravenous pyelogram, and lymphangiogram. Pretreatment ECG, audiogram, and nephrogram were recorded.

According to Wharton [21], the cytoreductive surgery performed followed the criteria of a simple tumor removal. The surgical procedures were either simple laparotomy with biopsies, partial excision of the tumor masses with removal of at least one ovary, or standard total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and

* Part of the work reported in this paper has already been presented at the AACR Meetings in 1980 in San Diego (Proc Am Assoc Cancer Res 21: 148, Abs. 595) and in 1981 in Washington DC (Proc Am Assoc Cancer Res 22: 166 Abs. 660)

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biopsies of any suggestive lesion. Lymph node biopsy or selective lymphadenectomy were performed only when indicated on the basis of the lymphagiogram or surgical evaluation. Restaging laparoscopy was performed in patients referred from other hospitals after primary surgery.

Patients were stratified according to the maximum diameter of the largest residual tumor lesion after primary surgery: stage III late when the largest lesion measured more than 2 cm in diameter; stage III early when the largest lesion measured less than 2 cm in diameter; stage III no residual when there was no macroscopic residual tumor.

Patients were assigned to receive adriamycin (A) and cyclophosphamide (C) in combination with hexamethylmelamine (H) (HAC) or *cis*-dichlorodiamineplatinum (P) (PAC) by selection of sealed randomized cards.

The *HAC regimen* consisted in H (150 mg/m^2 PO daily on days 1–14) in combination with A (50 mg/m^2 IV on day 1), and C (70 mg/m^2 PO daily on days 1–14).

The *PAC regimen* consisted in P (50 mg/m^2 IV as a 1-h infusion on day 1), in combination with A (50 mg/m^2 IV on day 1), and C (70 mg/m^2 daily on days 1–14, by the IV route on day 1 and PO on days 2–14).

Both regimens were repeated every 4 weeks.

The night before the administration of P, all patients received 2 l saline. In the 6 h after P infusion 1 l saline and 1 l 5% glucose containing 40 mEq KCl were given.

This protocol, applied to all patients, was modified on the basis of the diuresis (i.e., fluids were increased if diuresis was less than 100 ml/h in the 6 h after P, or if diuresis exceeded the volume of infused fluids. If a low urine output was not modified by the increase of fluids, patients received 12.5 g mannitol as an IV push).

If leukocyte or platelet counts were less than 3,000 cells/μl or 100,000/μl, respectively, 4 weeks after therapy, treatment was deferred for 1 week. After this time, if leukocyte or platelet counts were greater than 3,000 cells/μl or 100,000/μl treatment was resumed at the full dosage. If leukocyte or platelet counts were 2,000–3,000 cells/μl or 75,000–100,000/μl treatment was resumed at 50% dosage; if leukocyte or platelet counts were less than 2,000/μl or 75,000/μl no therapy was given, and treatment was further deferred until values rose over these thresholds. PAC administration was deffered for 2 weeks if serum creatinine was higher than 2 mg/100 ml or 24-h creatinine clearance was below 50 ml/min 4 weeks after the last treatment. If these values persisted after this delay, P was discontinued.

Physical and pelvic examination, complete blood count, biochemical tests, serum electrolytis, and 24-h creatinine clearance were repeated before each cycle of therapy. ECG, nephrogram, and audiogram were recorded every 3 months.

Patients were evaluable for response and toxicity when sufficient data were available for determining the effect of treatment after at least one cycle of chemotherapy. Response was assessed by clinical examination and surgical procedures (laparoscopy and/or laparotomy). A complete response (CR) was defined as disappearance of all evidence of disease on clinical examination or at careful restaging with second-look laparoscopy or laparotomy or both [25]; a partial response (PR) was defined as $\geq 50\%$ reduction of the total tumor size lasting at least 3 months, without progression of any lesion; no change (NC) was a $< 50\%$ decrease in the total tumor size for at least 3 months or a $< 25\%$ increase of one or more lesions; progressive disease (PD) was a $> 25\%$ increase in one or more lesions or the appearance of new lesions or effusions. Survival and duration of response were recorded from the first day of treatment.

Patients who achieved a clinical CR after incomplete initial surgery were submitted to laparoscopy and, when indicated, to laparotomy with debulking surgery before reaching a limiting dose of 450 mg/m^2 of A. Patients with no clinically evaluable disease response or with an uncertain clinical evaluation were checked by laparoscopy before the limiting dose of A.

Laparoscopy and/or laparotomy were repeated in responders when the limiting dose of A was reached. At this time, partial responders continued treatment with P and C or with H and C until progression, and complete responders started maintenance therapy with C only (70 mg/m^2 PO daily). Laparoscopic follow-up was repeated in responders at 18 and 24 monthts from the start of treatment; at this time patients still in CR confirmed by laparotomy stopped chemotherapy.

Statistical methods. Response rates and the other contingency tables were compared by the χ^2 test. Survival and time to progression curves were calculated by the method described by Kaplan and Meier [11]. These curves were statistically compared using the log-rank test and, when advisable, the test for trend [14]. All eligible patients were included in the survival curves.

Results

Of the 120 eligible patients who entered this trial between February 1978 and September 1980, 116 received at least one course of treatment and were evaluable for response, survival and toxicity. Out of four patients evaluable for survival and toxicity only, one died 14 days after the first HAC

Table 1. Characteristics of eligible patients

Characteristics	HAC[b]	PAC
Eligible for study	57	63
Median age in years (range)	54 (18–69)	53 (22–70)
FIGO stage		
III	53 (93)	59 (94)
IV	4 (7)	4 (6)
Histological type		
Serous	47 (82)	48 (76)
Mucinous	4 (7)	0 (–)
Endometrioid	3 (5)	8 (13)
Undifferentiated	3 (5)	7 (11)
Histological grade		
1	11 (19)	12 (19)
2	16 (28)	21 (33)
3	30 (53)	30 (48)
Initial surgery		
TAHBSO[a] plus omentectomy	23 (40)	30 (48)
Partial excision	19 (33)	12 (19)
Biopsy only	15 (26)	21 (33)
Residual postoperative tumor		
No residual	7 (12)	6 (10)
Early (< 2 cm)	10 (18)	11 (17)
Late (> 2 cm)	40 (70)	46 (73)

[a] TAHBSO, total abdominal hysterectomy bilateral salpingo-oophorectomy

[b] Figures in parentheses give percentages

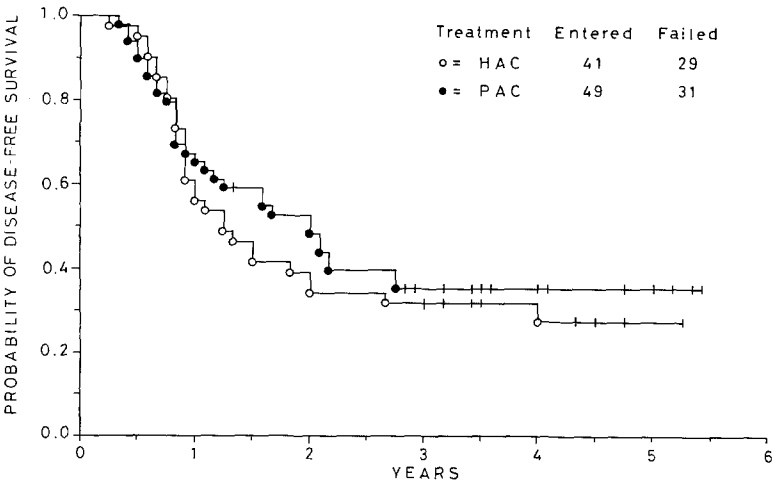

Fig. 1. Time to progression after treatment with HAC (○———○) or PAC (●———●) (CR, PR, NC)

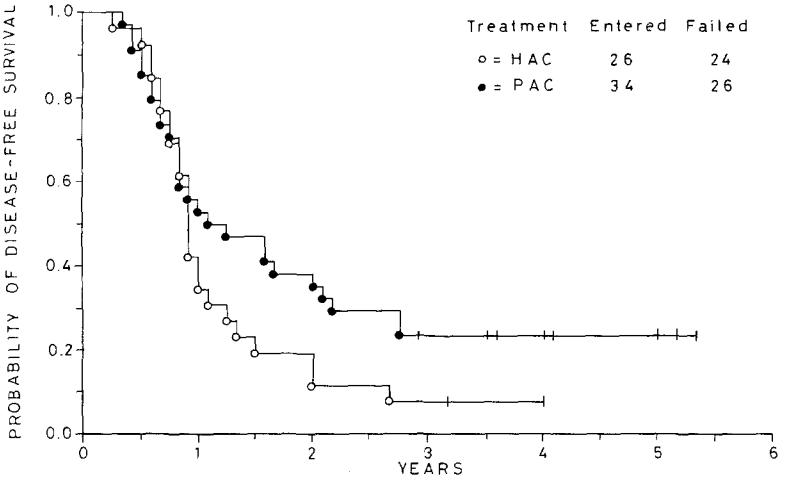

Fig. 2. Time to progression after treatment with HAC (○———○) or PAC (●———●) in patients with > 2 cm residual disease (CR, PR, NC)

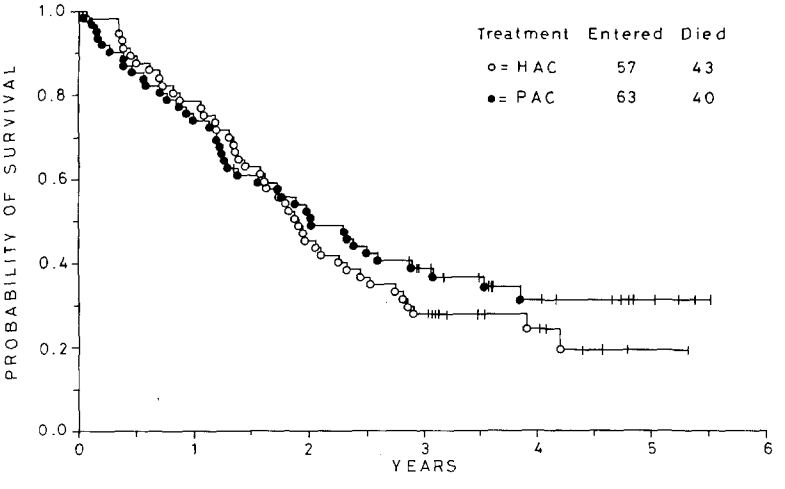

Fig. 3. Survival after treatment with HAC (○———○) or PAC (●———●)

dose from pneumonia *ab ingestis;* two patients treated with PAC died after the first cycle, one from neoplastic pulmonary embolism and one from sudden cardiac death, both confirmed by autopsy; one patient stopped therapy because of the appearance of atrial fibrillation after the first course of PAC.

The two treatment groups were well-matched for age, FIGO stage, histological type, histological grade, initial surgery, and extent of residual disease after initial surgery (Table 1).

Table 2 shows the response rate to HAC and PAC combination therapy according to residual tumor after initial surgery. In patients with residual tumor > 2 cm, the complete response rates to HAC and PAC were 13% and 21%, respectively. Of the 17 patients evaluated as partial responders to HAC one had only microscopic disease in the tissues

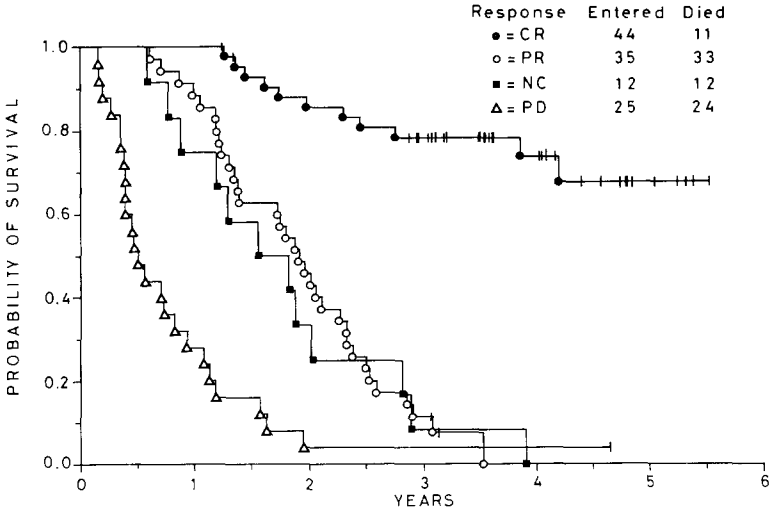

Fig. 4. Survival of patients with complete remission (CR) (●——●), partial remission (PR) (○——○), no change (NC) (■——■), or progressive disease (PD) (△——△)

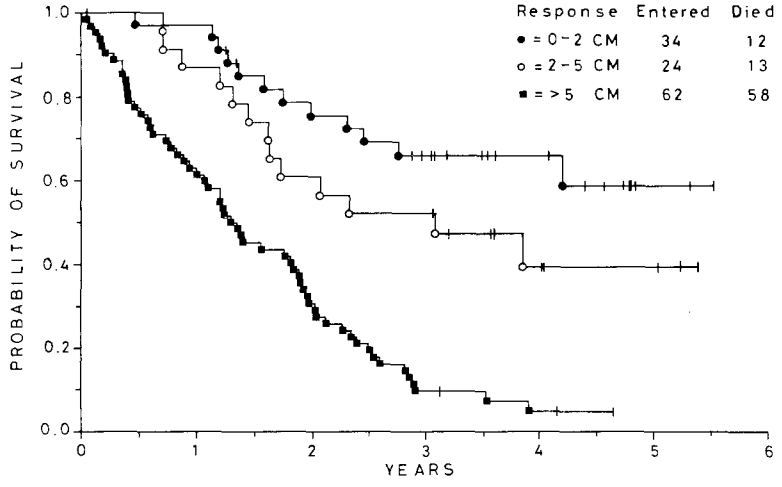

Fig. 5. Survival of patients according to maximum diameter of residual postoperative tumor: (●——●) 0–2 cm; ○——○, 2–5cm; ■——■, > 5 cm

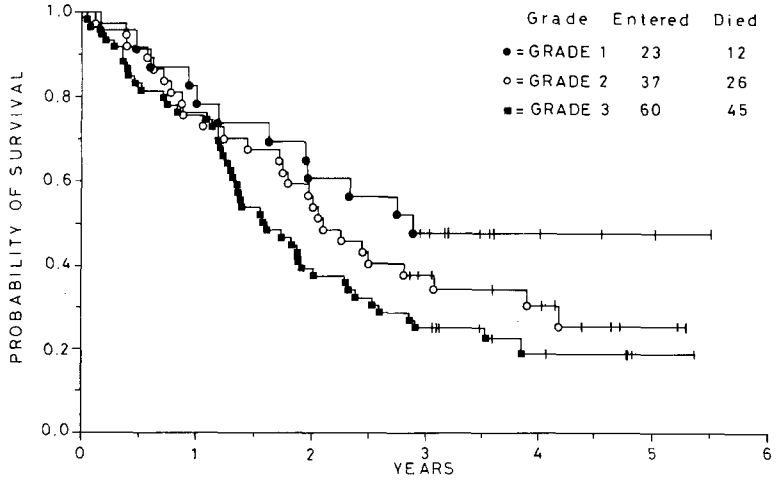

Fig. 6. Survival of patients according to histological grading: ●——●, grade 1; ○——○, grade 2; ■——■ grade 3

removed at second-look laparotomy and seven had incomplete resection of their tumor at second-look laparotomy after a median of eight cycles. Out of 18 partial responders to PAC, six patients had microscopic disease localized in ovaries, uterus, or omentum removed at second-look surgery, and partial resection of residual tumor was performed in four patients after a medium number of five cycles. The overall response rate (CR + PR) to HAC was 66% (56% in patients with > 2 cm residual tumor) and that to PAC, 70% (63% in patients with > 2 cm residual tumor).

In patients with > 2 cm residual disease, the median duration of CR was 25 months for the group treated with HAC; in two patients there has still been no progression at 38 and 48 months. The median duration of CR for the group treated with PAC has not yet been reached, because only one of nine patients relapsed at 33 months of follow-up, and in the

Table 2. Response to HAC and PAC therapy according to residual tumor after initial surgery[a]

	HAC				PAC			
	No residual	≤ 2 cm	> 2 cm	All patients	No residual	≤ 2 cm	> 2 cm	All patients
CR	6 / 0 (86)	9 / 0 (90)	5 (13) / 17 (44) (56)	20 (36) / 17 (30) (66)	6 / 0 (100)	9 / 0 (82)	9 (21) / 18 (42) (63)	24 (40) / 18 (30) (70)
NC	0	0	5	5 (9)	0	0	7	7 (12)
PD	1	1	12	14 (25)	0	2	9	11 (18)
Total	7	10	39	56	6	11	43	60

[a] Figures in parentheses are percentages

Table 3. Hematological toxicity of HAC and PAC treatment

Toxicity	HAC (%)	PAC (%)
Leukopenia (cells/μl)		
3,000–< 4,500	42	53
2,000–< 3,000	29	27
1,000–< 2,000	4	3
Thrombocytopenia		
90,000–< 130,000	19	27
50,000–< 90,000	15	3
25,000–< 50,000	–	–
Anemia (g/100 ml)		
9.5–< 11	31	41
< 9.5	13	24
Hemoglobin drop > 2 g/100 ml	27	38
Required transfusion	6	15

Table 4. Nonhematological toxicity of HAC and PAC treatment

Side effects	HAC (%)	PAC (%)
Nausea	52	–
Nausea and controllable vomiting	35	–
Intractable vomiting	–	100
Alopecia	100	100
Stomatitis	8	2
Cystitis	10	7
Allergic reactions	6	17
Peripheral neurotoxicity	38	41
Headache	6	–
Nephrotoxicity (maximum serum creatinine > 1.2 mg)	–	24
Ototoxicity (> 30 db loss at 6,000–8,000 Hz)	–	35[a]

[a] 35% out of the 28 patients who were followed by serial audiograms

other eight there has still been no progression at follow-up times ranging from 35 to 64 months. The median duration of PR was similar in the two groups (11 months for HAC and 12 months for PAC). In patients assessed as NC after HAC and PAC treatment, median times to progression were 7 and 6 months, respectively.

With either therapy, the median time to progression was in excess of 38 months for complete responders (in excess of 42 months in patients with > 2 cm residual disease); 11 months for partial responders; and 6 months for patients with stable disease (log-rank test and test for trend were both significant at $P < 0.00005$).

Median times to progression were 14 months in the HAC and 22 months in the PAC group (log-rank $P = 0.5$) (Fig. 1), decreasing to 11 and 13 months in patients with > 2 cm residual disease (log-rank $P = 0.13$) (Fig. 2).

There was no difference in the overall median survival of the two treatment groups (23 months for HAC and 24 months for PAC) (log-rank $P = 0.45$) (Fig. 3). The median survival time in patients with > 2 cm residual disease was 20 months after HAC and 20 months after PAC.

Survival was analyzed according to response at surgical restaging in each treatment group. The median survival of complete responders has not been reached, but will exceed 39 months for the patients treated with HAC and 44 months for the patients treated with PAC. Partial responders to HAC and PAC had a median survival of 23 and 21 months, which is no different from that of patients evaluated as NC to the same treatment (22 months). The median survival times of patients with PD were 9 and 5 months, respectively. Figure 4 summarizes survival according to response without regard to the type of therapy. Analysis of the survival according to response in patients with > 2 cm residual tumor showed the same significant trend. In each treatment group there was a significant trend between reduction of the median survival time and increase of the maximum diameter of residual disease after surgery (log-rank test and test for trend both significant at $P < 0.00005$). Figure 5 presents the overall survival analyzed according to the diameter of residual tumor without regard to type of therapy.

In each treatment group there was a similar but not statistically significant correlation between survival and histological grading, median survival time increasing at the lower tumor grades (Fig. 6).

Table 3 outlines the hematological toxicity in this study, assessed from the blood cell counts on the day before each course. Myelosuppression was generally mild and similar in the two arms. One or more delays in treatment because of leukopenia were required in 21% of HAC and 14% of PAC patients. No patient had leukopenia of less than 1,000 cells/μl.

The nonhematological toxicity is summarized in Table 4. Respectively 6% and 17% of patients treated with HAC and PAC had local allergic reactions to A, manifested as an erythematous rash along the vessel during injection, reversible within 1 h. Administration of hydrocortisone before subsequent courses prevented the recurrence of this effect. Peripheral neurotoxicity, consisting in mild bilateral paresthesia, occurred in 38% and 41% of patients, respectively, treated with HAC and PAC. It appeared after a mean of five cycles of

HAC and a mean cumulative dose of 300 mg/m^2 P (range 100–500 mg/m^2), gradually increased during treatment, and slowly regressed after discontinuation of the drugs. In 6% of patients, H treatment was associated with recurrent headache. No patient showed a rise of the serum creatinine value above 2 mg/100 ml. Hearing loss, defined as a more than 30 decibel loss at 6,000–8,000 Hz, occurred in 35% of patients checked by audiograms, after a mean cumulative dose of 400 mg/m^2 P (range 350–550 mg/m^2).

Discussion

At a follow-up time of 36 months, the results of this study show that in previously untreated ovarian cancer PAC is as effective as HAC in terms of response, duration of remission, and survival. The results in the PAC group (70% of overall response rate, 40% of complete remissions documented by surgical restaging, 21% of complete remissions in patients with >2 cm residual disease, median time to progression and median survival time of 22 and 24 months) are similar to those previously reported with the same combination [4, 20]. Our results with HAC (66% overall response rate; 36% complete remissions documented by surgical restaging; 13% complete remissions in patients with >2 cm residual disease; median time to progression and median survival time of 14 and 23 months) are comparable with those obtained by Edwards et al., who found comparable activity for HAC and the combination of melphalan and *cis*-platinum [7].

As already reported [1, 4, 7, 20, 25], patients who achieve a CR with chemotherapy alone have better chances of long-term survival than patients in whom the CR was obtained by removal of organs still containing microscopic disease after treatment. All the seven patients in this study who had microscopic disease in the tissues excised at second-look laparotomy relapsed after a median progression-free interval of 24 months (range 13–26 months) and a median survival time of 31 months (range 28–43 months). However, second-look surgery plays a role in prolonging the survival only of those clinical complete responders in whom it is possible to excise the residual tumor totally [16, 17, 19]. In this study, the median duration of remission and the median survival time of patients classed as achieving PR to chemotherapy did not appear to be improved by partial resection of the neoplasia leaving macroscopic residual disease.

Second-line activity of multidrug regimens in patients failing with previous combination chemotherapy is very limited [7, 15]. The discouraging results with cisplatin-CAF and Hexa-CAF as salvage therapies in patients failing or relapsing with HAC and PAC, respectively [18], again stress that only the 'true' complete responders to first-line chemotherapy benefit with prolonged survival.

It is accepted that in previously untreated ovarian cancer NC corresponds to a failure of treatment; therefore, patients with stable or progressive disease were always analyzed together as nonresponders to first-line chemotherapy. In this study, patients showing NC after treatment had median survival comparable to that of PR patients and significantly longer than patients with PD. This relatively long survival of patients with stationary disease was not due to subsequent effective treatment; none of them responded to second-line therapies. Although no characteristic common to these patients could be identified (age, histological type, or grade), these results suggest that stable disease is representative of a particular class of ovarian cancer patients with slow-growing tumors resistant to chemotherapy, and should be therefore analyzed separately in the evaluation of treatment.

Histological grading and extent of residual disease after initial surgery are important prognostic factors for response and survival in advanced ovarian cancer [4, 7, 10, 13, 20, 25]. The present study confirms a relation between reduction of the survival time and increase of the tumor diameter above 2 cm for both therapies tested. With either type of therapy, the median survival time appeared shorter to a similar extent in patients with higher histological grade tumors.

In patients with >2 cm residual disease, the roles played by H and P in the HAC and PAC combinations appear important. If we compare the results of these three-drug combinations with those previously reported by the same group with A C, using the two drugs at the same dosages and applying the same criteria for response assessment [2], the CR rate and survival differ in favor of the three-drug regimens. However, the use of a historical control and the unbalanced distribution of the histological grading in the populations evaluated in the two studies do not permit any statistically reliable conclusion.

In patients with >2 cm residual disease, HAC and PAC both gave a CR rate $>80\%$, showing activity similar to that reported with different combinations in comparable groups of patients [2, 6, 9, 25]. Multidrug therapy appears to be potentially curative in patients with minimal residual disease, as suggested by the high percentages of CR, resulting in an improvement of the median survival time compared with patients with extensive residual disease. The small number of patients tested in each series and the short follow-up time do not permit us to establish which is the more effective regimen in limited stage III ovarian cancer. Nevertheless, the late relapses observed in this study suggest that new effective approaches are required to increase the cure rate further in this favorable group of patients.

In this study, HAC and PAC treatment caused mild hematological toxicity. The 4-week interval between PAC courses avoided the severe hematological toxicity observed when the same drug doses were administered at 3-week intervals [8]. The 35% asymptomatic ototoxicity in the PAC group was higher than previously reported; it occurred especially in the complete responders who received the whole of the planned treatment program, thus confirming that this toxicity is related to the cumulative dose at least in the regimen using P at relatively low doses.

The results of this study suggest that HAC and PAC combinations are similarly effective in advanced ovarian cancer, the follow-up time being too short and the number of complete responders too small to permit conclusions on longer survival after PAC. Though these results justify some optimism with regard to a possible increase in the cure rate in this generally fatal malignancy, the large proportion of relapses already observed suggests caution and must therefore prompt further experimental and clinical research to find new, better therapies.

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