fixed complete heart block may be a phase in the natural history of the development of idiopathic heart block.

In our study the results of 24 h ECG monitoring did not differ greatly between group 1 (symptomatic athletic patients) and group 2 (symptom-free normal athletes). Apart from the exceptional case 16 in group 1, we found only 2 patients with documented ventricular pauses longer than 2·5 s.

Clinical appreciation of loss of consciousness and accompanying symptoms led us to label the syndrome in group 1 as cardiac syncope and/or Stokes-Adams attacks. Prolonged absence of pulse was witnessed clinically in 2 patients. The complete disappearance of syncope in patients given pacemakers further supports the diagnosis of cardiac syncope. Symptoms subsided completely in 8 unpaced patients; acceleration of basic heart rhythm after they stopped competitive sports is likely to be the reason for the relief of symptoms. This result accords with the findings of Meytes[15] and Rasmussen.[13] The life-threatening condition required pacemaker implantation in 7 patients in group 1. The question of whether these patients will need pacemakers all their lives remains; it must be answered by a future generation of cardiac pacemakers with built-in Holter facilities.

The normal athlete does not suffer from any discomfort correlated with bradycardia, pauses, or both. We believe that there is no reason for warnings against competitive sports. Recent case-reports and rumours tend to myth.[17] In our group 2 athletes we found only minor abnormalities. Schnohr obtained information about 297 (96·7%) of 307 male athletic champions born in Denmark between 1880 and 1910 and compared their mortality with that in the general Danish male population.[18] The athletic champions had a significantly lower mortality than the general population under the age of 50 years; after 50 years of age the mortality was the same. The causes of death were the same as in the general population.

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RANDOMISED TRIAL COMPARING TWO COMBINATION CHEMOTHERAPY REGIMENS (HEXA-CAF VS CHAP-5) IN ADVANCED OVARIAN CARCINOMA

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Summary 186 patients with advanced epithelial ovarian carcinoma were treated with either a combination of hexamethylmelamine, cyclophosphamide, methotrexate, and 5-fluorouracil (Hexa-CAF) or cyclophosphamide and hexamethylmelamine alternating with doxorubicin and a 5-day course of cisplatin (CHAP-5). Treatment with CHAP-5 resulted in more complete remissions as determined by laparatomy or peritoneoscopy ($p = 0 \cdot 004$), better overall response ($p = 0 \cdot 0001$), and longer overall survival and progression-free survival ($p < 0 \cdot 002$). Therapy, histological grade, and Karnofsky index were reliable predictors of overall response, whereas therapy, FIGO-stage, and size of residual tumour before chemotherapy were independent predictors for complete remission and for prolonged survival. Peripheral neurotoxicity was a major problem in patients assigned to the CHAP-5-group and was likely to be due to the simultaneous administration of hexamethylmelamine and cisplatin. The CHAP-5 regimen is one of the most effective regimens for the initial treatment of ovarian cancer.

Introduction

IN many Western countries ovarian cancer is the commonest cause of death among women with gynaecological neoplasms. Most patients present with tumour extension beyond the pelvis or positive retroperitoneal nodes (FIGO[1] stage III) or with distant metastases (FIGO stage IV). The prognosis for these patients has been poor. In about 40% the tumour responds to a single alkylating agent and the median survival time is approximately 14 months. In patients who go into remission survival is prolonged, but only a small percentage will survive in the long term. The overall 5-year survival rate is less than 10%.[2] Several non-alkylating drugs have shown activity in ovarian cancer patients. Patients resistant to alkylating agents, may respond to 5-fluorouracil,[3] methotrexate,[4] hexamethylmelamine,[5] cis-platinumdiamminedichloride (cisplatin),[6-8] and doxorubicin.[9-11] Unfortunately, these responses were not sustained and there were no long-term survivors. Better results were obtained when these agents were used in previously untreated patients. Investigators from the National Cancer Institute have reported that the four-drug combination of hexamethylmelamine, cyclophosphamide, methotrexate, and 5-fluorouracil (Hexa-CAF) gives better results than an alkylating agent (melphalan) alone.[12] The four-drug regimen resulted in a higher

percentage of remissions and a longer median survival. In our experience the regimen gave a somewhat lower response rate and was rather toxic.[13] We thought that the regimen might be more acceptable if it could be made less myelotoxic, so we modified the dose of cyclophosphamide and took the Hexa-CAF regimen as a standard treatment against which to compare other new regimens.

Other promising regimens for the treatment of ovarian cancer are those that include cisplatin. These combinations have produced response rates of up to 90%.[14] However, there were no comparative studies to indicate that combinations incorporating cisplatin were superior to combinations without it. That was why, in 1979, we started a randomised study comparing Hexa-CAF with a four-drug combination regimen (CHAP-5) that included cisplatin. The drugs in the CHAP-5 schedule (cyclophosphamide, hexamethylmelamine, doxorubicin, and cisplatin) are not cross-resistant and are known to be active in ovarian cancer when used alone.[5,7-11,15] To avoid overlap of toxicity and to ensure that optimum doses could be given, the drugs were given as separate alternating combinations: doxorubicin plus cisplatin (AP) and cyclophosphamide plus hexamethylmelamine (CH). We report here our findings. The data enabled us to analyse the prognostic factors for women treated with combination therapy, the relation between prognostic factors, and the impact of surgery on treatment results.

Subjects and Methods

Protocol Entry Criteria

Only patients with histologically verified epithelial ovarian cancer stage III or IV (FIGO classification) were included in the study. Patients were excluded if they were older than 70, had serious cardiac disease, active second tumour, brain metastases, creatinine clearance of less than 70 ml/min, or previous chemotherapy or radiotherapy. The staging had to have been done in the 6 weeks before entry. At the start of chemotherapy the haematological status had to be favourable (at least 3000 leucocytes/μl and more than 75 000 platelets/μl). Follow-up had to be feasible.

Pre-treatment Staging

Before treatment, the extent of the disease and the amount of tumour present had to be established definitely, and as many tumour variables as possible were listed. The extent of the disease was determined by surgical exploration via a median lower and upper abdominal incision. As much of the tumour as possible was removed, and a total abdominal hysterectomy, a bilateral salpingo-oophorectomy, and a complete infracolic omentectomy were done. Suspect lymph nodes and suspected liver abnormalities detected by palpation were biopsied. Before chemotherapy was initiated, each patient underwent a complete blood count, liver and renal function tests, a chest X-ray, intravenous pyelography, electrocardiography, and audiometry. In addition most patients were examined by ultrasonography, computerised tomography, and lymph-angiography for tumour localisation.

Histology and Grading

All histological specimens were classified by a pathology review committee and categorised according to the World Health Organisation classification.[16] The histological grade of the specimens was based on the percentage of undifferentiated cells present and the degree of anaplasia (modified Broder's grades 1-4).[17,18]

Randomisation

Allocation of patients to treatment group was based on a telephone call to a centre that held a random selection of sealed envelopes.

TABLE I—PROTOCOL FOR DOSAGE MODIFICATION OF THE DRUGS

Leucocytes (/μl)	Platelets (/μl)	Dosage modification (percentage of dose to be given)					
		ADR	DDP	CYC	HMM	FU	MTX
>4000	>120 000	100	100	100	100	100	100
3000–4000	75 000–120 000	50	100	50	100	50	50
<3000	<75 000	Stop*	Stop	Stop	Stop	Stop	Stop

Abbreviations: ADR = doxorubicin; DDP = cisplatin; CYC = cyclophosphamide; HMM = hexamethylmelamine; FU = 5-fluorouracil; MTX = methotrexate. Dose must be adjusted weekly during drug administration.

*Stop treatment: Wait for 2 weeks before starting the next treatment cycle with Hexa-CAF and for 1 week before starting CHAP-5. Reinstitute treatment only in case of recovery. Otherwise, wait another week. If the CHAP schedule is interrupted during treatment with cyclophosphamide and hexamethylmelamine, re-start schedule with the adriamycin/cisplatin part of the cycle.

Drug Regimens

Patients assigned to the Hexa-CAF regimen received methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2, both given intravenously on days 1 and 8. Cyclophosphamide 100 mg/m^2 and hexamethylmelamine 150 mg/m^2 were each given orally on days 1 to 14. On days 15 to 28 no drugs were given. After that the cycle was repeated.

Patients on CHAP-5 received doxorubicin 35 mg/m^2 on day 1 as an intravenous bolus injection before the administration of cisplatin. Cisplatin 20 mg/m^2 was given intravenously on days 1 to 5. The drug was administered as a 4 h infusion in 1 litre of normal saline, immediately following hydration with 1 litre normal saline. Post-hydration consisted of an infusion of 2 litres of normal saline. If diuresis was less than 600 ml per 6 h or the fluid retention was more than 1500 ml in 24 h, 5 to 10 mg frusemide was given intravenously. Starting from day 15, hexamethylmelamine 150 mg/m^2 and cyclophosphamide 100 mg/m^2 were both given orally for 14 days. In the last week no therapy was given. Thereafter, the regimen was repeated starting on day 36 with doxorubicin and cisplatin again.

When myelosuppression occurred, the dose was modified as shown in table I. If during treatment the white-cell count dropped below 1000/μl or the platelet count below 20 000/μl the prescribed doses of doxorubicin, methotrexate, 5-fluorouracil, and cyclophosphamide were reduced by 25% for subsequent cycles.

Assessment of Response

Patients with clinically evaluable tumour masses underwent restaging and second-look laparotomy upon attaining clinically complete remission. In most cases the procedure was preceded by laparoscopy. Those with clinically non-evaluable tumours were restaged surgically after 6 cycles of chemotherapy. After restaging, treatment was as follows: patients in surgically complete remission received 6 further cycles of chemotherapy if toxicity permitted; those with microscopic disease only, or partial remission, received 6 cycles and then were staged again; patients with a stable, non-resectable tumour were allowed to leave the study; and those whose disease had progressed also left the study.

Therapy was terminated: if a third-look operation showed no improvement since the second-look laparotomy, or if treatment had been interrupted as a result of toxicity for more than 6 weeks.

All patients were evaluated by physical examination and by haematological, renal, and hepatic function tests before each cycle of chemotherapy. Chest X-ray, electrocardiography, creatinine clearance, and measurement of the tumour diameter by ultrasound were performed every 3 cycles. Computerised tomography was performed after 6 cycles or when indicated.

Cytoreductive Surgery

Maximum "debulking" (the removal of as much tumour as possible) was recommended for all patients before the start of chemotherapy. In those patients in whom debulking was not performed initially, maximum debulking took place as soon as chemotherapeutic reduction rendered the tumour masses resectable (intervention debulking surgery). Debulking procedures were performed in the cooperating institutions.

Definitions of Tumour Response

A complete clinical remission was defined as complete regression of all clinically detectable tumour for at least 1 month. A complete remission at peritoneoscopy was said to be reached when, at restaging peritoneoscopy, intraperitoneal washings and biopsy specimens were microscopically free of tumour. A complete remission established at laparotomy meant that during extensive surgical restaging, no tumour was detectable and washings and multiple biopsy specimens were negative for tumour.

When no tumour was seen macroscopically but intraperitoneal washing fluid or biopsy specimens showed tumour cells on microscopy, the remission was termed microscopic disease. A partial response was defined as a decrease of more than 50% in the sum of the products of the perpendicular diameters of measurable lesions plus a complete regression of malignant effusions persisting for at least one month. No change or stable disease was defined as an absence of increase in measureable disease and no increase in malignant effusions persisting for at least one month. Progressive disease was defined as a 25% or greater increase of the measurable tumour size or the appearance of new lesions.

Salvage Treatment

Patients for whom Hexa-CAF or CHAP-5 chemotherapy failed were offered alternative treatment. Patients who did not respond to Hexa-CAF were offered a variety of chemotherapy regimens that included cisplatin (such as cisplatin, vinblastine, bleomycin; cisplatin, adriamycin; cisplatin alone).

Patients who did not respond to CHAP-5 received chemotherapy consisting of methotrexate, 5-fluorouracil or new drugs undergoing phase I or phase II investigation. Patients with small tumour masses were given with appropriate doses of radiotherapy.

Evaluation and Statistical Methods

Patients were considered evaluable for response and toxicity when sufficient data were available for determining the effect of treatment after at least one cycle of chemotherapy. Survival time was defined as the period that elapsed between the start of chemotherapy and death. Time to disease progression was also counted as from start of chemotherapy. All eligible patients were included in the survival curves. Patients who died of causes other than ovarian cancer were not excluded from the analysis. Patients who died without disease progression were excluded from the progression-free survival curves at the end of the observation period. Cases withdrawn from the study not because of progression (ie, because of toxicity) were dropped from the analysis from the day that a new therapeutic regimen was started. Survival distributions were described by the product limit method, and the generalised Wilcoxon (Breslow) statistics were used for testing the difference between the curves. The relation between a set of covariates and response was estimated in the multivariate setting by the use of the stepwise logistic regression method.[19] The effect of prognostic factors and other covariates on survival function was determined by the use of the proportional hazard regression model.[20] Use was made of the P1L, P2L, and PLR programme of the BMDP statistical software package.[21] All p values in the tables are two-sided tests.

Toxicity is reported according to the recommendations of the World Health Organisation.[22] Renal function was monitored by serial determination of the serum creatinine level. The serum creatinine level was determined before, during, and after each treatment cycle.

Results

Patient Population

Between March, 1979, and May, 1981, 196 patients were enrolled. Of these 10 patients were not eligible. Cut-off date for analysis was December, 1983, median follow-up being 39 months and longest follow-up 53 months. The characteristics of the patients eligible for study are summarised in table II. The different variables were equally distributed between the two treatment groups.

Treatment Results

In 103 patients, a second-look procedure was indicated because they went into clinically complete remission, but in 3 the procedure was not feasible. 78 second-look laparotomies, 22 second-look laparoscopies, and 15 third-look laparotomies were performed to assess the final response.

In 40% of the patients (37 out of 103) who were clinically free of disease, a complete remission was confirmed at second-look procedure. The size of residual tumour found on inspecting the abdominal cavity was of prognostic significance. In none of the patients was the prognosis changed by removal of remaining tumour.

All 186 patients eligible for the study were analysed for survival. Median survival was 23·8 months and median time to disease progression 12·2 months. Overall survival and progression-free survival were significantly longer for the CHAP-5 than for the Hexa-CAF group (fig 1). Median survival data are summarised in table III. The survival benefit in patients receiving CHAP-5 was significant in those with a FIGO-stage III ($p = 0 \cdot 005$), but not in patients with a FIGO-stage IV ($p = 0 \cdot 3$), tumour.

The final response obtained with both therapies is shown in table III. The number of complete remissions documented at laparotomy or peritoneoscopy ($p = 0 \cdot 004$) and the overall response rate ($p < 0 \cdot 0001$) were higher in CHAP-5 than in the

TABLE II—CHARACTERISTICS OF PATIENTS ELIGIBLE FOR STUDY ACCORDING TO TREATMENT

Characteristics	Hexa-CAF	CHAP-5
Eligible for study	94	92
Mean age (yr)	53·5	53·5
Mean Karnofsky index	87	87
FIGO stage		
III	67 *(71)*	63 *(69)*
IV	27 *(29)*	29 *(32)*
Histological type		
Serous	45 *(48)*	44 *(48)*
Mucinous	8 *(9)*	7 *(8)*
Endometrioid	5 *(5)*	9 *(10)*
Clear cell	5 *(5)*	0 *(0)*
Undifferentiated	10 *(11)*	16 *(17)*
Unclassified	21 *(22)*	16 *(17)*
Histological grade		
1	16 *(19)*	11 *(13)*
2	24 *(28)*	25 *(30)*
3	33 *(38)*	29 *(35)*
4	11 *(13)*	14 *(17)*
Unclassified	2 *(2)*	4 *(5)*
Missing	8	9
*Residual tumour before chemotherapy**		
Microscopic	5 *(5)*	3 *(3)*
<1 cm	13 *(14)*	13 *(14)*
1–2 cm	9 *(10)*	14 *(15)*
2–5 cm	20 *(21)*	21 *(23)*
>5 cm	47 *(50)*	41 *(45)*

Unless indicated otherwise, the numbers refer to the number of patients with the characteristic mentioned. Figures in parentheses denote percentages.
*Largest cross-sectional diameter.

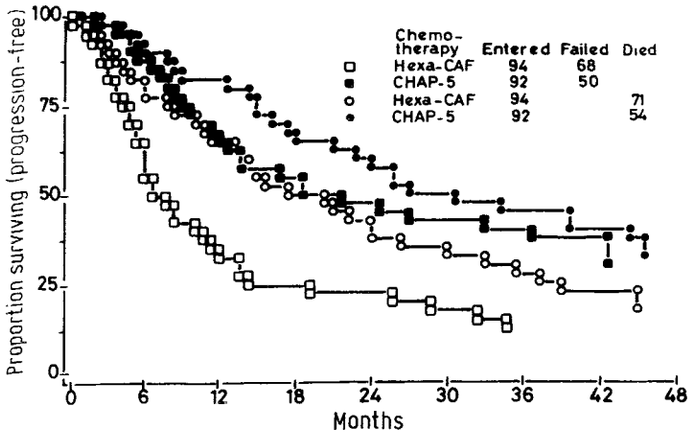

Fig 1.—Survival (circles) and progression-free survival (squares) after treatment with Hexa-CAF (open symbols) or CHAP-5 (closed symbols).

Hexa-CAF group. Tumour progression despite therapy occurred in 32% of the Hexa-CAF and only 11% of the CHAP-5 patients. Survival and progression-free survival were analysed in relation to response. 63% of the patients treated with CHAP-5 who were found to be in complete remission at laparotomy were alive and disease-free 3 years after the onset of chemotherapy, as were 44% of the patients in complete remission after treatment with Hexa-CAF. Of the 68 patients who "failed" (ie, whose disease relapsed or progressed) with Hexa-CAF 13 went into partial remission or stable disease after salvage therapy. None of the patients who failed with CHAP-5 went into remission.

Prognostic Factors.

Survival curves were determined for several possible prognostic factors. Curves were influenced by FIGO stage

TABLE III—HEXA-CAF AND CHAP-5: RESULTS OF THERAPY

Results	Therapy		p-value
	Hexa-CAF	CHAP-5	
Patients evaluable for response	88	84	
No with response	44 *(50)*	66 *(79)*	0·0001
Complete remission (L)	15 *(17)*	25 *(30)*	<0·05
Complete remission (P)	2 *(2)*	8 *(10)*	<0·05
Microscopic disease	6 *(7)*	8 *(10)*	
Partial remission	21 *(24)*	25 *(30)*	
No change	16 *(18)*	9 *(11)*	
Median duration of:			
Progression-free survival (mo)	6·8	19·5	<0·0001
Overall survival (mo)	19·6	30·7	<0·002

Figures in parentheses denote percentages.
L = laparotomy;
P = peritoneoscopy.

TABLE IV—PROGNOSTIC VALUE OF PRETREATMENT PATIENT CHARACTERISTICS FOR OBTAINING RESPONSE, COMPLETE REMISSION DOCUMENTED AT LAPAROTOMY, OR LONG SURVIVAL

Pretreatment characteristics	Response* (144 patients)	Complete remissions at laparotomy* (172 patients)	Prolonged survival† (146 patients)
Therapy	p<0·001	p=0·001	p=0·01
Age	NS	NS	NS
Weight	NS	NS	NS
Karnofsky index	p=0·026	NS	NS
FIGO stage	NS	p=0·004	<0·001
Histological type	NS	NS	NS
Histological grade	p=0·020	NS	NS
Size of residual tumour	NS	p<0·001	p=0·03
Leucocyte count	NS	NS	NS

Significance levels (two-sided) obtained by logistic regression* or by χ^2 test.†

(difference between III and IV), p=0·0008; Karnofsky index, p=0·001; age (below or above 45), p=0·05; and size of the residual tumour before chemotherapy, p=0·01. The size of the residual tumour before chemotherapy, cytostatic treatment, and FIGO-stage are predictors for prolonged survival and for a complete remission documented at laparotomy (table IV). Patients who were treated with Hexa-CAF and had residual tumour of less than 1 cm in FIGO-stage III had a 29% chance (4/19) of being found to be in complete remission at laparotomy, whereas treatment with CHAP-5 offered them a 67% chance (8/12). Therapy, histological grade, and the Karnofsky index are independent predictors for overall response. 94% of patients with grade 4 tumours and a good Karnofsky index responded to chemotherapy.

The prognostic variables mentioned above were related to some other factors (table V). Patients with a high Karnofsky index had high pretreatment body weight and total leucocyte counts, were young, and generally had small residual tumours before chemotherapy. Those in FIGO stage III, or who had highly differentiated endometrioid, mucinous, or serous tumours also had a high Karnofsky index. Histological grade 1 tumours were commoner in young patients, whereas unclassified and grade 2 tumours were seen more often among older subjects.

Surgery

Overall patients whose tumours had been reduced to less than 1 cm diameter by cytoreductive surgery before chemotherapy survived longer than patients with larger residual tumours; the difference was also significant in the CHAP-5 group (p=0·004) but not in the Hexa-CAF group (p=0·11) (fig 2). The survival for patients who had residual tumours with diameters between 1 and 2 cm was similar to that for patients who had larger tumour remnants (p=0·335).

TABLE V—RELATION BETWEEN DIFFERENT PROGNOSTIC VARIABLES

	Age	Weight	Karnofsky Index	FIGO stage	Histological type	Histological grade	Residual tumour
Age	–						
Weight	NS*	–					
Karnofsky index	p=0·04*	p=0·05*	–				
FIGO stage	NS	NS	p<0·001	–			
Histological type	NS	NS	p=0·04	NS*	–		
Histological grade	p=0·01	NS	p=0·02	NS	p<0·001*	–	
Residual tumour	NS	p=0·05*	p=0·01*	NS	NS	NS	–
Leucocyte count	NS*	NS*	p=0·03*	NS	NS	NS	NS*

*Statistical test: Pearson correlation coefficient. The remaining p-values are calculated with the F-test.
NS = not significant.

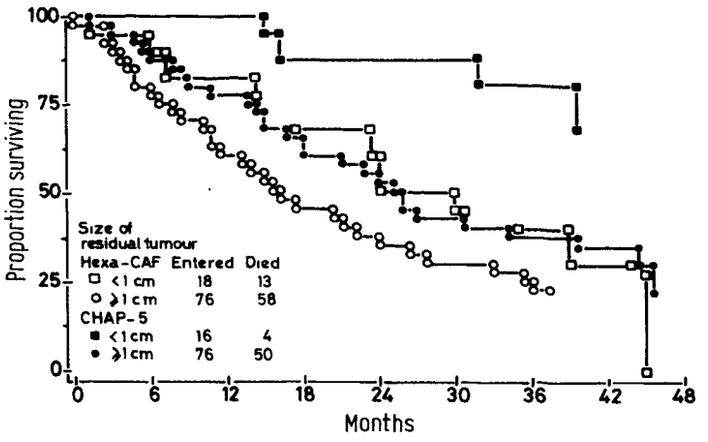

Fig 2.—Survival following treatment with Hexa-CAF or CHAP-5 according to tumour size before start of chemotherapy.

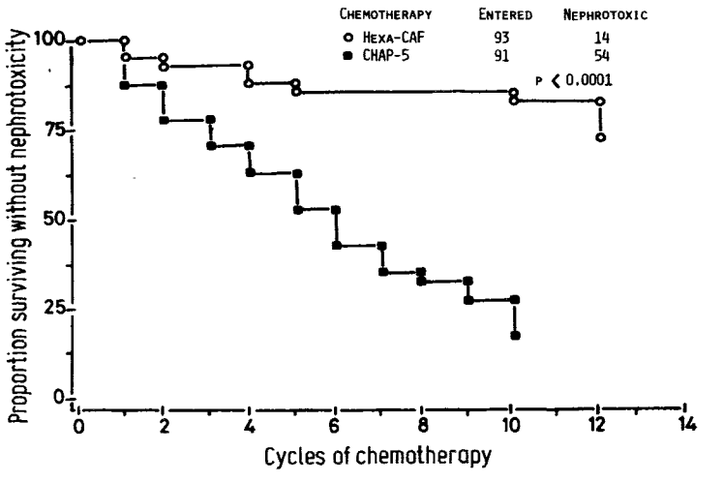

Fig 3.—Nephrotoxicity-free survival following treatment with Hexa-CAF and CHAP-5.

Patients are recorded as nephrotoxic when serum creatinine exceeds 1·25 times the pre-treatment serum creatinine value.

In 15 of the patients on Hexa-CAF and 18 on CHAP-5 an operation was performed while they were on chemotherapy, to remove as much tumour as possible (cytoreductive intervention surgery). When intervention surgery reduced tumour size to less than 1 cm, survival was prolonged ($p = 0 \cdot 02$). Patients who underwent successful cytoreductive intervention surgery had almost the same chance of survival as those who underwent successful cytoreductive surgery before chemotherapy ($p = 0 \cdot 22$).

Toxicity

93 patients treated with Hexa-CAF and 91 patients treated with CHAP-5 were evaluable for toxicity (table VI). Neurotoxicity occurred in both treatment groups and consisted mainly of peripheral neuropathy. Paraesthesias of the fingers and toes were followed by motor weakness. The lower extremities were more seriously affected than the upper extremities. In patients assigned to CHAP-5, the frequency of mild or moderate neurotoxicity increased after 4 cycles of chemotherapy to approximately 50% after the 6th cycle.

The mean serum creatinine level increased steadily with each course of CHAP-5. After 6 treatment cycles the serum creatinine had risen by 25% above the pretreatment level in 50% of the patients who received CHAP-5 (fig 3). There was no relation between the cycle number and frequency of rises in creatinine levels. No relation could be demonstrated between the time at which serum creatinine level rose and the pretreatment serum creatinine level, pretreatment creatinine clearance, or the age of the patient. Infections, mucositis, bleeding episodes, cardiac function disturbance, and allergic manifestations were equally rare for both regimens.

TABLE VI—NUMBER OF PATIENTS WITH SIDE-EFFECTS

Toxicity	Hexa-CAF (n=93)	CHAP-5 (n=91)
Nausea and vomiting		
Mild	33 *(36)*	8 *(9)*
Moderate	25 *(27)*	41 *(45)*
Severe	28 *(30)*	38 *(41)*
Hair loss		
Mild	16 *(17)*	7 *(8)*
Moderate	14 *(12)*	11 *(15)*
Complete	25 *(27)*	55 *(60)*
*Peripheral neurotoxicity**		
Mild	18 *(19)*	15 *(16)*
Moderate	3 *(3)*	32 *(35)*
Severe	0 *(0)*	4 *(4)*
Renal toxicity†		
Moderate	13 *(14)*	50 *(55)*
Severe	1 *(1)*	4 *(4)*
Anaemia (mmol/l)		
6·8–5·8	21 *(23)*	35 *(38)*
5·8–4·9	7 *(8)*	23 *(25)*
<4·9	2 *(2)*	8 *(9)*
Leucopenia (×10⁹/l)		
4·0–3·0	12 *(13)*	6 *(7)*
3·0–2·0	28 *(30)*	27 *(30)*
2·0–1·0	27 *(29)*	50 *(55)*
<1·0	10 *(11)*	5 *(6)*
Thrombocytopenia (×10⁹/l)		
100–75	9 *(10)*	23 *(25)*
75–50	10 *(11)*	14 *(15)*
50–25	4 *(4)*	21 *(23)*
<25	6 *(6)*	6 *(7)*

Figures in parenthesis denote percentages.
*Peripheral neurotoxicity: mild = mild paresthesias or decreased tendon reflexes, moderate = moderate paresthesias or mild weakness, severe = severe intolerable paresthesias, marked motor loss.
†Renal toxicity: moderate = the serum creatinine exceeds 1·26–2·5 times the pre-treatment value, severe = 2·6–5 times the pre-treatment value.

In 25 patients, all on CHAP-5 therapy, treatment was discontinued because of toxicity—neuropathy in 16 patients, persistent thrombocytopenia for more than 6 weeks in 5, ototoxicity in 2, persistent leucopenia in 1, and nephrotoxicity in 1. 1 patient died probably because of toxicity. Most patients in both regimens required dosage reduction or treatment delay because of toxicity. In the Hexa-CAF schedule the overall mean dose administered of cyclophosphamide, hexamethylmelamine, methotrexate, and 5-fluorouracil were respectively: 65, 85, 70, and 70% of the prescribed dosage. Patients on CHAP-5 received cisplatin at approximately full dose (96%) and hexamethylmelamine on average at 82%. More intensive dosage reduction was required for doxorubicin and cyclophosphamide (overall 75% and 56% of the prescribed dosage could be given respectively), in keeping with the requirements of the protocol for toxicity. In both patient groups the mean dosages of cyclophosphamide and hexamethylmelamine were gradually decreased in subsequent management cycles. Hexa-CAF patients received respectively 84, 82, 75, 73, 73, and 69% and CHAP-5 patients, respectively, 79, 70, 74, 68, 66, and 64% of the prescribed dosage of both drugs.

The effect of dosage and cycle duration on the treatment results was analysed in a multivariate setting. Neither the interval between the different treatment cycles nor dosage influenced treatment outcome.

Discussion

Our comparison of Hexa-CAF with CHAP-5 showed that remission rate, number of complete remissions, duration of progression-free survival, and duration of survival were significantly better with CHAP-5. This is the first time that one schedule (CHAP-5) has been shown to lead to better survival times than another combination (Hexa-CAF); Hexa-CAF is at least as good as standard alkylating therapy. A variety of combination chemotherapy regimens have been used to treat ovarian cancer. These regimens improve remission rates, number of surgically proven complete remissions, and duration of progression-free survival, compared with standard alkylating agents, but do not improve overall survival.[23] Only three studies have claimed that the regimen tested influenced survival positively. Young and co-workers have reported a significantly better survival after treatment with Hexa-CAF than with melphalan, but their results have been criticised on statistical grounds,[24,25] and could not be confirmed by other groups.[26,27] The Swedish Cooperative Ovarian Cancer Study Group conducted a randomised trial to compare the effects of melphalan with those of a doxorubicin/melphalan combination and reported a significantly better survival for the combination.[28] However, these results have to be regarded with caution because at least 3 other randomised studies could not confirm the findings.[28–31] A randomised comparison between treatment with cyclophosphamide alone in 21 patients and that with cyclophosphamide and cisplatin combined in another 21 patients showed better survival with the combination ($p = 0 \cdot 01$),[32] but it is not clear whether or not patients who experienced a relapse on cyclophosphamide received salvage treatment that included cisplatin.

In our study the better survival with CHAP-5 than with Hexa-CAF is not due to insufficient second-line treatment of the latter group. All eligible patients were offered salvage treatment that included cisplatin, and their overall response rate was about 20%. These results are comparable with those seen in other alkylator-resistant patients who received salvage chemotherapy that included cisplatin.[33,34] We can only speculate on why the CHAP-5 regimen has been so successful when other studies have not been able to show that a similar drug combination prolongs overall survival.

The Eastern Cooperative Oncology Group used a combination consisting of cisplatin 50 mg/m^2 intravenously on day 1, adriamycin 25 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 intravenously on day 1, and hexamethylmelamine 150 mg/m^2 orally on days 8–21 (CHAD). The schedule was repeated after 4 weeks. They compared CHAD prospectively with melphalan. An interim report indicated a significantly higher response rate and longer progression-free survival with the combination, but no advantage in duration of survival.[33] This disparity between their results and ours may be due to the difference in dosage and the method of administration. Our patients on CHAP-5 received twice the dose of cisplatin, more doxorubicin, and more cyclophosphamide. Cisplatin, which is the drug of choice for ovarian cancer, could be given in nearly full doses throughout the treatment.

The predictive factors for complete remission and for survival were the same—therapy, FIGO-stage, and tumour size after staging laparotomy. FIGO-stage had a greater effect on survival than did therapy, but therapy influenced survival more than did surgery before chemotherapy. The best long-term prognosis is seen in patients treated with CHAP-5, FIGO-stage III, and only a small residual tumour mass. Every degree of tumour reduction by surgery before initiation of therapy enhances the probability of a sustained complete remission. The effect of cytoreductive surgery was greater for CHAP-5 than for Hexa-CAF patients, indicating that extensive debulking is only of benefit when the procedure is followed by treatment with powerful drugs. Although age and histological grade have been found to be of long-term prognostic significance,[18,33,35,36] we concluded that they are less important than stage and size of residual tumour before chemotherapy. However, the tumour grade is an important factor in predicting the response to chemotherapy, as is performance status. The difference in survival between patients under and those over 45 years of age was due to the small size of the residual tumour before chemotherapy, the more favourable histological grading, and the good performance status of the younger patients. The difference between survival of subgroups with different Karnofsky scores is explained by the relation between the Karnofsky index and stage. Most patients with low performance status had stage IV disease.

The CHAP-5 regimen appears to be more toxic than the Hexa-CAF regimen, partly because it was given for a longer time, which in turn was because patients in CHAP-5 had a longer progression-free survival. With both schedules the main reason for dosage modification was myelosuppression. Only in a minority of patients was myelosuppression a limiting factor, so our conclusion is that myelosuppression is a fairly important but manageable side-effect. Peripheral neuropathy was a major problem in the CHAP-5 group, and was most likely to be due to the administration of hexamethylmelamine and cisplatin in one schedule. In the patients assigned to the CHAP-5 group, the incidence of neurotoxicity increased rapidly after four cycles of chemotherapy. A rapid increase in neurotoxicity after approximately 500 mg/m^2 cisplatin has also been reported by the MD Anderson group.[7] Renal toxicity was mild. Our results show that cisplatin given in 5 low daily doses is tolerated very well, even after high cumulative dose of cisplatin.

CHAP-5 thus seems to be one of the most effective regimens nowadays for the treatment of ovarian cancer. The schedule is rather toxic but side-effects can be managed and the regimen is easy to apply in daily practice. Without new active agents further improvement of the treatment results will be difficult. More aggressive surgery and the introduction of new approaches, such as intraperitoneal chemotherapy, may improve the outlook for patients with epithelial ovarian carcinoma.

We thank Mr A. J. de Meyer, Miss E. Hamersma, and Prof A. Struyvenberg for their contribution to this study.

This study was supported in part by the Netherlands Cancer Society (Stichting Koningin Wilhelmina Fonds).

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WHO COOPERATIVE TRIAL ON PRIMARY PREVENTION OF ISCHAEMIC HEART DISEASE WITH CLOFIBRATE TO LOWER SERUM CHOLESTEROL: FINAL MORTALITY FOLLOW-UP

Report of the Committee of Principal Investigators*

Summary This is the final report on mortality amongst men in the WHO cooperative trial of the prevention of ischaemic heart disease (IHD) by clofibrate and it takes the follow-up a further 4 years to the end of 1982. Mean observation was 13·2 years, 5·3 in the trial and 7·9 afterwards. 1788 deaths were recorded in 208 000 man-years. In the 877 new deaths reported here, there was an excess of 9 deaths in the high cholesterol control group compared with the clofibrate-treated group. In the whole period there were 70 (11%) more deaths in the clofibrate-treated group. Excess mortality in the clofibrate-treated group was much greater during the "treatment period" (there was an excess of 47% during treatment compared with 5% after treatment had ended) and was due to a wide variety of causes other than IHD. Thus, the excess mortality in the clofibrate-treated group has not continued after the end of treatment. The substantial excess previously reported remains unexplained.

Introduction

THE results of the WHO cooperative trial of the prevention of ischaemic heart disease (IHD) by clofibrate were published in 1978.[1] There was a 25% reduction ($p<0·05$) in non-fatal myocardial infarction among healthy men with plasma cholesterol in the upper third of the distribution who were given clofibrate, compared with randomly selected controls. There was no significant difference in mortality from IHD.

Mortality from all causes and causes other than IHD was significantly higher in the clofibrate-treated group. No particular disease accounted for the overall excess, there being non-significant increases in cancer, and other major diseases, though not in deaths due to accidents and violence. There was also a significant excess in the death-rate from all causes, and from causes other than IHD, in the treated group compared with a second, low cholesterol, control group after correction for differences in age and other factors present at the start of the trial.

The first report of post-trial follow-up, to the end of 1978, was published in 1980.[2] It showed 25% more deaths in the clofibrate-treated group than in the comparable, high serum cholesterol, control group ($p<0·01$). This excess mortality was most marked for deaths which occurred during the trial (an average period of 5·3 years). No relation could be shown between excess mortality in the treated group and either cholesterol reduction during the trial or the length of time that subjects were receiving clofibrate.

These results were sufficiently disturbing to warrant a follow-up of mortality for a further 4 years, to the end of 1982,

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