PAPERS AND SHORT REPORTS

High dose cisplatin compared with high dose cyclophosphamide in the management of advanced epithelial ovarian cancer (FIGO stages III and IV): report from the North Thames Cooperative Group

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Abstract

A randomised study comparing cisplatin 120 mg intravenously with cyclophosphamide 2 g intravenously, each drug being given every month for six months followed by a low dose regimen for a further six months in responding patients, was carried out in 86 patients with advanced epithelial ovarian carcinoma (FIGO stages III and IV).

Patients given cisplatin were found to have a longer median survival time than those given cyclophosphamide (19 months compared with 12 months) and a longer median duration of complete clinical response (18 months compared with eight months). The difference in disease free survival was statistically significant even after factors such as age, stage of disease, and the completeness of initial surgery had been taken into account.

This study suggests that cisplatin is a more effective chemotherapeutic agent than cyclophosphamide for advanced ovarian cancer and should be the agent of choice in future trials comparing combination chemotherapy with a single agent.

Introduction

Alkylating agents have been used for many years in the treatment of advanced carcinoma of the ovary with reported objective

response rates of 35-65% and 5-15% of all patients maintaining a response after two years.¹ Cisplatin (*cis*-dichlorodiammine platinum (II)), introduced more recently, has been used mainly in combination with other agents—for example, cyclophosphamide and doxorubicin (Adriamycin).²⁻³ It has also been claimed to be effective as a single agent in patients resistant to alkylating agents,⁴⁻⁵ but it has rarely been used as a single agent in patients previously untreated with chemotherapy.⁶ No randomised trial has been reported comparing cisplatin as a single agent with an alkylating agent such as cyclophosphamide used at high dose.

The North Thames Cooperative Group, inaugurated in 1980, is composed of medical practitioners with an interest in gynaecological cancer. In 1980 a study was begun to determine whether cisplatin administered as a single agent is more effective than high dose cyclophosphamide for advanced epithelial carcinoma of the ovary, FIGO (International Federation of Gynaecology and Obstetrics) stage III or IV. An additional aim was to assess whether patients who had failed to respond to one drug could be salvaged by the other.

Materials and methods

Patients with stage III or IV carcinoma of the ovary and who were less than 75 years of age were eligible. Epithelial carcinomas of the following histological types were included in the trial: serous, mucinous, endometrioid, mesonephroid, mixed epithelial, undifferentiated; all other tumours, including borderline malignancy, were excluded. In all cases the histological findings were reviewed by two pathologists (Dr M Anderson, Dr J Beilby).

All patients were randomised after surgery—but before review of the histological findings by the pathology panel—to receive either cisplatin or cyclophosphamide. Before treatment the following investigations were carried out: full blood count; measurement of urea and electrolytes, serum creatinine, creatinine clearance, and liver function values; chest radiography; and examination of midstream specimen of urine. Optional investigations not part of the trial protocol included lymphangiography and isotope liver scans. Patients were assessed clinically and by ultrasound or computed tomography (CT), if available, every three months, and if there was no response or if there was progression

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or recurrence of disease the patient was switched to the other drug (fig 1). After six courses of chemotherapy participating gynaecologists were requested to carry out "second look" surgery—either laparoscopy or laparotomy—to assess progress in responding patients. If response was confirmed the patient received a further six months of chemotherapy at the lower dose. At the end of 12 courses of treatment a further laparoscopy or laparotomy was recommended for patients continuing to show a complete clinical response (fig 1). Complete clinical response was defined as no clinical evidence of disease detected by physical examination, chest radiography, ultrasound, etc.

The initial recommended surgery was hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy (optimal surgery), but this could not be carried out in all patients (suboptimal surgery). Second look laparotomies were recommended where optimal surgery had not initially been performed to see if further debulking could be carried out and in cases where para-aortic nodes

were known to be affected. Most other patients had a laparoscopy with peritoneal washings and biopsy of suspicious lesions.

Cisplatin was given intravenously once every four weeks at a dose of 120 mg in 1 litre isotonic saline administered over six to eight hours with a sedative—for example, lorazepam—and antiemetics—for example, metoclopramide. Three to four litres of isotonic or dextrose saline was given in 24 hours both before and after the infusion to maintain a urine output of 100 ml hourly. Potassium supplements and diuretics were used as indicated. Magnesium supplements were not used routinely. After six courses in responding patients the dose was lowered to 30 mg every four weeks to avoid severe cumulative toxic effects, peripheral neuropathy in particular.

Cyclophosphamide was given intravenously every four weeks at a dose of 2 g, 1 g being given as an intravenous bolus on two consecutive days with hydration as described above with cisplatin. This "high dose" regimen was carried out for a total of six courses. "Low dose" cyclophosphamide was given as an intravenous bolus of 1 g every four weeks.

Toxicity was carefully noted and treatment given in a reduced dosage as indicated to patients with low blood counts (white cell count less than $3.0 \times 10^9/l$ or platelet count less than $100 \times 10^9/l$) or evidence of renal impairment (creatinine clearance < 50 ml/min). If renal impairment was severe (creatinine clearance < 30 ml/min or serum creatinine concentration twice the normal value for the referring centre) treatment was discontinued.

Statistical analysis—Survival and duration of response curves were calculated using standard life table techniques⁷ and statistical significance determined by the log rank method.⁸ Adjustment of life tables for factors thought to affect survival or duration of response was made using the method of Hankey and Myers, which also provides statistical evaluation of adjusted curves via an adjusted χ^2 statistic.⁹ The significance of differences in the proportions of patients between two groups was evaluated using the Fisher exact test.¹⁰

Results

A total of 117 patients with stage III or IV epithelial ovarian carcinoma were entered into the trial between April 1980 and September 1982. Twenty five patients were excluded after randomisation when review indicated inappropriate histological findings. A further six patients were also excluded because they were found after randomisation to be less than stage III or died before receiving any chemotherapy. This left 86 patients for analysis, 37 of whom drew cyclophosphamide and 49 cisplatin. Table I gives the characteristics of the patients. Sixty five patients were stage III and 21 stage IV. All surviving patients remained in the trial for a minimum of two years. Their ages ranged from 39 to 75 years (median of 55). Optimal surgery (hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy) was carried out in 42 of the 86 patients. Of the variables recorded—age, stage of disease, and surgery—only optimal surgery was found to be unevenly allocated between the two treatment groups, 26 (53%) of patients who had drawn cisplatin having received optimal surgery compared with 16 (43%) of patients who had drawn cyclophosphamide. In addition, 11 out of 12 grade 1 tumours were in the platinum treated group, but analysis of this apparent disparity showed it to be not significant.

Table II shows the median survival times and durations of response. The median survival for all patients was 14 months. Patients who received optimal surgery before chemotherapy had a median survival of 26 months compared with only 12 months when optimal surgery could not be carried out. Patients who drew cisplatin had a median survival of 19 months compared with 12 months for cyclophosphamide.

A total of 45 patients (52%) achieved a complete clinical response,

FIG 1—Flow chart of trial.

TABLE 1—Patient characteristics

Drug	No of patients aged:		FIGO stage		Histological type of tumour						Grade			Optimal surgery*	Second look surgery
	>60	<60	III	IV	Serous	Mucinous	Endometrioid	Mesonephroid	Mixed	Undifferentiated	1	2	3		
Cisplatin (n = 49)	17	32	37	12	23	9	6	4	1	6	11	21	17	26	26
Cyclophosphamide (n = 37)	12	25	28	9	16	2	4	4	1	10	1	16	20	16	11
Total (n = 86)	29	57	65	21	39	11	10	8	2	16	12	37	37	42	37

*Optimal surgery: hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy.

TABLE II—Median survival times and durations of complete clinical response

	Median survival (months)	Median duration of complete clinical response (months)
All patients	14	13
Optimal surgery	26	18
Suboptimal surgery	12	11
Drew cisplatin	19	18
Drew cyclophosphamide	12	8

the rate being significantly higher in the patients treated with cisplatin (31/49 *v* 14/37; $p=0.03$).

Patients treated with cisplatin survived significantly longer than those treated with cyclophosphamide ($p=0.009$) (fig 2). The duration of response, both complete and partial (defined as $>50\%$ reduction in tumour size as estimated by clinical examination, ultrasound, etc), was also significantly longer in the cisplatin arm ($p=0.006$) (fig 3). This effect remained when the curves were adjusted for optimal surgery, though significance was less ($p=0.04$), reflecting the imbalance in numbers receiving optimal and suboptimal surgery between the two groups. The equivalent curves for complete clinical response (fig 4) did not reach statistical significance but showed the same trend in favour of cisplatin.

Patients who received optimal surgery before chemotherapy survived significantly longer than those given suboptimal surgery ($p=0.006$) (fig 5), and this effect was independent of treatment group (adjusted p value = 0.009). Figure 6 shows a similar comparison, but for complete responders only, no significant difference being apparent.

FIG 2—Actuarial survival times in cisplatin and cyclophosphamide treatment groups.

FIG 3—Durations of clinical response (complete and partial) in the two treatment groups.

FIG 4—Durations of complete clinical response in the two treatment groups.

FIG 5—Actuarial survival times after optimal (debulking) and suboptimal (non-debulking) surgery.

Patients over 60 were less likely to achieve a response (complete or partial) than those under 60 ($p=0.04$), but survival subsequent to response was independent of age.

Second look surgery (laparoscopy or laparotomy) was carried out in 37 patients, 26 of whom had drawn cisplatin and 11 cyclophosphamide (table I). Of the 26 patients who had drawn cisplatin, complete clinical response was confirmed surgically in 16. Six of these patients were examined at six months only, and two of these subsequently died (10 months and 15 months). The 10 others were examined at six months and one year; of these, one died at 25 months and one had a recurrence at 40 months. Among the patients who drew cyclophosphamide, six of the 11 who had second look surgery had their complete response confirmed—one at six months (who subsequently died at 15 months) and five at one year (one of whom died at 14 months).

Patients who failed to respond to the initial treatment did not do well when the alternative drug was given. Of the 49 originally treated with cisplatin, six were changed to cyclophosphamide because of failure to respond. None, however, had a further response. Of the 37 patients treated with cyclophosphamide, 15 were changed because of lack of response, but none achieved complete clinical response with cisplatin.

The amount of residual tumour left in surgically debulked patients was considered but sufficient information was available in only 33 patients. Five had no residual tumour after surgery, and four of these showed complete clinical response at one year. Nine of 18 patients with residual tumour up to 5 cm diameter, and none of the 10 patients with residual tumour greater than 5 cm diameter, achieved complete clinical response.

The most common epithelial tumours were serous cystadeno-

carcinomas (39 cases)—of which seven were well differentiated in comparison with five out of 11 mucinous cystadenocarcinomas. Sixteen patients had undifferentiated tumours, 10 endometrioid, and the remainder mesonephroid or mixed epithelial, none of which were well differentiated. Histological type and grade were not found to be significant factors with regard to response to treatment and survival in this series.

The quality of life of patients was closely associated with the state of their disease. Those with a complete clinical response were able to lead almost normal lives, some of whom continued to work throughout their period of treatment. In responding patients, however, the quality of life was affected by vomiting, the main toxic effect of both cyclophosphamide and cisplatin. This was particularly severe with cisplatin.

Hair loss was recorded in 23 (62%) of the patients receiving cyclophosphamide, of whom six had severe alopecia, and in 15 (31%) of the patients receiving cisplatin alone, but hair loss was severe in only one of these patients. Renal toxicity with chemotherapy was reported in 16 patients, 11 of whom had received cisplatin. The cisplatin treated patients showing renal toxicity initially had the dosage reduced, and in four patients treatment was switched to cyclophosphamide. Haematological toxicity—defined as a haemoglobin concentration below 10 g/dl—was reported in seven patients while receiving cisplatin and two cyclophosphamide, but falls in the white cell or platelet count were never reported as severe enough to warrant a dose reduction. Peripheral neuropathy occurred in three patients receiving cisplatin as the "low dose" regimen. Cyclophosphamide toxicity included one case of allergic reaction and two of haematuria but transfusion was not required.

FIG 6—Durations of complete clinical response after optimal and sub-optimal surgery.

Discussion

In view of the lack of studies comparing single agents for advanced ovarian cancer we decided to examine in a randomised controlled study the individual value of two commonly used chemotherapeutic agents before embarking on combination chemotherapy. An increase in clinical response rate has been observed using combination chemotherapy compared with a single alkylating agent, but an increase in patient survival has not been shown.^{11 12} The single exception was a study comparing melphalan with hexa-CAF (hexamethylmelamine, cyclophosphamide, methotrexate, and fluorouracil).¹³ This difference was not confirmed by others comparing high dose intravenous cyclophosphamide with hexa-CAF.¹⁴

The optimal dose and frequency of administration required for cytotoxic agents in ovarian cancer is unknown. In the case of cisplatin high dose therapy has been found to give a higher response rate.¹⁵ A high response rate with weekly cisplatin has been found in patients resistant to previous chemotherapy, and weekly cisplatin is now being used as induction treatment in untreated patients with advanced ovarian cancer.¹⁶ In this trial

we opted for 120 mg given every four weeks because we had found that higher doses caused peripheral neuropathy in some patients. For a true comparison between two drugs it is important that they are given by the same route, and thus both cisplatin and cyclophosphamide were given intravenously.

The aim of chemotherapy is to eliminate all residual disease left after surgery. While clinical examination and routine investigations such as chest radiography will detect gross recurrence and further information is obtained when ultrasound and CT are added, for deposits of less than 1 cm or residual microscopic disease second look surgery with biopsy is the most accurate method of detection and should be used in assessing clinical response in prospective randomised trials. In this trial laparoscopy with peritoneal washings was carried out more frequently than laparotomy because, notwithstanding the reported greater accuracy of laparotomy,¹⁷ most participating gynaecologists considered laparotomy to carry too great a morbidity. While partial response may increase the quality of a patient's life, it will not lead to long term survival.² Hence the only response of value in assessing treatments of ovarian cancer is complete clinical response confirmed surgically. In this trial cisplatin induced more complete clinical responses confirmed surgically than cyclophosphamide. The value of surgical complete response in predicting prolonged survival was confirmed in our series but the numbers were small.

The importance of cytoreductive surgery for long term survival has been emphasised.^{18–20} In this study survival was greater in patients who had had a hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy. The extent of initial surgery did not significantly affect duration of response in patients who achieved a complete clinical response, although the numbers were small and follow up was not long enough to compare proportions of long term survivors.

The importance of verifying the diagnosis of ovarian epithelial carcinoma when conducting trials was confirmed in this trial, as 21% of cases had to be withdrawn on pathological grounds, the most frequent problems being of "unknown origin," primary tumour in the bowel, and borderline malignancy. The importance of pathological type and grade of tumour has been studied by Dembo and Bush²¹ as part of a multivariate analysis to define good and poor prognostic groups in ovarian cancer. In their series grade was not of prognostic value in mucinous, endometrioid, and clear cell tumours but was highly predictive in serous cystadenocarcinoma, in that moderately and poorly differentiated tumours responded badly compared with well differentiated ones. In analysing our own series grade of tumour was not found to be a relevant factor.

At present prolongation of survival is difficult to obtain in most patients with advanced ovarian cancer, and when these patients are treated the quality of their lives must be taken into account. In this series the quality of life of patients who achieved complete clinical response was good. It was notable that several of the younger patients returned to full time work while receiving treatment, although psychological problems in continuing treatment were present in most patients after six months. Patients with bulk disease not responding to chemotherapy found the side effects of treatment an additional burden to their remaining life. This factor must be taken into consideration before continuing with cytotoxic treatment in non-responders.

In conclusion, our study shows the importance of comparing single agents before embarking on trials comparing a single agent with combination chemotherapy. As cisplatin gave a longer disease free survival than cyclophosphamide it would appear that cisplatin rather than an alkylating agent is the drug of choice both when a single agent is used in the treatment of advanced ovarian carcinoma and when comparisons are to be made between combination therapy and a single drug. While a recent study²² comparing a combination regimen containing cisplatin (CHAP 5) with hexa-CAF showed a longer median disease free survival in the cisplatin group, it remains to be proved whether such a combination is superior to cisplatin alone or whether it merely adds increased toxicity and expense.

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The Tromsø heart study: coffee consumption and serum lipid concentrations in men with hypercholesterolaemia: a randomised intervention study

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Abstract

In a 10 week trial to assess the effects of coffee consumption and coffee brewing methods on serum cholesterol concentrations 33 men with hypercholesterolaemia were randomly assigned to: continue with their usual coffee intake; stop drinking coffee altogether; or stop drinking coffee for five weeks, thereafter drinking either boiled or filter coffee.

Cholesterol concentrations fell significantly in all subjects abstaining for the first five weeks compared with subjects not giving up and continued to fall in those abstaining for 10 weeks. Cholesterol concentrations rose

again in subjects returning to boiled coffee but remained the same in those returning to filter coffee.

Abstention from heavy coffee drinking is an efficient way of reducing serum cholesterol concentrations in men with hypercholesterolaemia. The extent to which the brewing method affects this relation requires further study.

Introduction

Two recent reports have linked coffee consumption with serum cholesterol concentration.^{1 2} Findings in both studies were based on consumption of black, boiled coffee. The only other study of this relation in man of which we are aware confirms these findings.³ Here we report a study to assess the effect on blood lipid concentrations of: (1) abstention from coffee in men with hypercholesterolaemia and (2) brewing coffee in two different ways.

Subjects and methods

The participants originated from a multifactorial intervention study of 1373 men at high risk of heart disease, aged 35-54, initiated during

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