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Randomised trial comparing prednimustine with combination chemotherapy in advanced ovarian carcinoma

Robert C. F. Leonard[1], George E. Smart[2], Jeremy R. B. Livingstone[2], Michael A. Cornbleet[1], Gillian R. Kerr[1], Stewart Fletcher[3], John N. Webb[4], and John F. Smyth[1]

[1] Department of Clinical Oncology, Western General Hospital, Crewe Road, Edinburgh, Scotland, UK
[2] Department of Obstetrics & Gynaecology, Royal Infirmary, Edinburgh
[3] University Department of Pathology, Medical School, Edinburgh
[4] Department of Pathology, Western General Hospital, Edinburgh

Summary. A total of 76 patients with advanced epithelial ovarian carcinoma were randomised to receive 6 months of treatment with either a combination of hexamethylmelamine, 5-fluorouracil, cisplatin and prednimustine or prednimustine alone following initial surgery. Pathologically confirmed response rates were 35% for combination chemotherapy and 28% for prednimustine, and the overall survival was identical for the two groups. Seven patients achieved a pathologically defined complete response, one of whom relapsed at 8 months; the others remain disease-free 18–36 months (median, 23 months) after presentation. The extent of initial surgery significantly affected the survival of patients receiving prednimustine but not of those receiving combination chemotherapy. Prednimustine can produce durable responses in advanced ovarian cancer using a schedule that results in negligible toxicity.

Introduction

Ovarian carcinoma has the highest mortality of any gynaecological cancer. Over the last 70 years there has been a 6-fold increase in its incidence, and 60%–70% of patients present with surgically incurable disease. The main determinants of survival in patients with advanced disease have been reported to be age, histological grade, the extent of tumour metastases, sites involved and extent of initial surgery [16].

Prior to the advent of cytotoxic chemotherapy, mortality at 5 years reached 100%. Since useful cytotoxic agents have become available, the importance of adequate initial surgery has become apparent. There is a clear relationship between the extent of initial surgical tumour removal (debulking) and the subsequent success of cytotoxic chemotherapy [12, 16] that translates into long-term survival [3]. The results of postoperative chemotherapy are best evaluated by second-look surgery, although the timing of the latter remains controversial. Second-look surgery gives the additional opportunity for the removal of remaining tumour tissue, although its therapeutic benefit is as yet not clear.

A number of studies have investigated the role of intensive chemotherapy in the management of advanced ovarian cancer since the first reports from the National Cancer Institute (NCI) (USA), which showed that the drug combination hexamethylmelamine, cyclosphosphamide, methotrexate and 5-fluorouracil (HexaCAF) gave better results than the alkylating agent melphalan alone [19]. The HexaCAF regime reslted in a higher percentage of remissions and a longer median survival than melphalan alone. After cisplatin was identified as a particularly useful agent for the treatment of ovarian cancer, the CHEX-UP combination incorporating cisplatinum, hexamethylmelamine, 5-fluorouracil and cyclophosphamide replaced HexaCAF in the subsequent NCI study [20].

In the present study we modified the CHEX-UP regimen by replacing cyclophosphamide with prednimustine (P-HEXUP). Prednimustine is a chemical ester of prednisolone and chlorambucil that has been reported to have activity in several types of human cancer, notably lymphoma, breast and ovarian carcinoma [5–8, 10]. In Johnsson's study of 36 previously untreated patients with advanced ovarian cancer, 2 complete and 8 partial clinical remissions were seen, for an overall response rate of 28%. We compared the activity of P-HEXUP with prednimustine alone, analysing the presenting features, existence of any prognostic factors, impact of initial surgery, toxicity and results of treatment.

Subjects and methods

Entry criteria demanded that only patients with histologically proven epithelial carcinoma of the ovary with a life expectancy >2 months, an age <70 years and FIGO stages 3 and 4 disease be included. Prior radiotherapy or chemotherapy excluded patients from the study. Patients were stratified for randomisation according to age ($\geqq 60$ or <60 years) and histological grade (good, moderate or poor). Prior to entry, the histological grade was confirmed by one of two pathologists (JW or SF); pretreatment investigations included a full blood count and biochemistry, creatinine clearance, chest radiology, IVU, lymphangiography, ultrasound scan of the upper abdomen and, if relevant, audiometry.

Drug regimes. Combination chemotherapy comprised 15 mg/m^2 prednimustine and 150 mg/m^2 hexamethylmelamine orally daily between days 2 and 15, and 600 mg/m^2 5-fluorouracil and 30 mg/m^2 cisplatinum i.v. on days 1 and 8. After 2 weeks of treatment, the cycle was recommenced and six cycles were scheduled at monthly intervals

Offprint requests to: R. C. F. Leonard

before reassessment of response. The following regimen for the administration of i.v. drugs was used: 5-fluorouracil was given at the beginning of i.v. hydration with 1 l dextrose saline (containing 30 mEq potassium chloride) over 6 h followed by 500 ml 10% mannitol containing 30 mg/m^2 cisplatin given over 30–60 min; this was followed by 1.5 l dextrose saline (containing 30 mEq potassium chloride per litre) over 17 h. Antiemetic therapy routinely consisted of high-dose metoclopramide with dexamethasone [5, 7]. Prednimustine as a single oral agent was given at 130 mg/m^2 daily for 5 days every 3 weeks. Blood counts were measured prior to each treatment and dose modifications were made accordingly.

Assessment of response. Disappearance of all assessable disease on clinical and radiological examination constituted a complete clinical response (CR) and demanded full appraisal by second-look laparotomy, which was carried out on all patients who were clinically disease-free at 6 months after the commencement of therapy. A partial response (PR) was defined as a decrease of >50% in the sum of the products of perpendicular diameters of measurable lesions plus a complete regression of any malignant effusions persisting for at least 1 month. Failure to fulfil these response criteria constituted a non-response (NR), and clinical progression (or surgical progression at second-look laparotomy) constituted progressive disease (PD).

Initial surgery. Whenever possible, maximal debulking (the removal of as much tumour as possible) was recommended for all patients before the start of chemotherapy, although repeat operations to attempt further debulking were not carried out prior to chemotherapy.

Evaluation and statistical methods. Patients were considered evaluable for response and toxicity if they met the above-mentioned eligibility criteria and received at least one cycle of chemotherapy. Survival was determined from the date of operation until death. The time until disease progression was counted from the start of chemotherapy. All eligible patients were included in the survival curves. Actuarial survival rates were calculated from Kaplan Meir curves and compared using the log-rank test [9, 13]. The effect of prognostic factors on survival was determined by the proportional hazard regression model [2]. Toxicity was recorded according to the recommendations of the World Health Organisation.

Restuls

Patient population

Between January 1981 and January 1984, 80 patients were randomised. Of these, four subsequently proved to be ineligible for the trial due to prior cytotoxic chemotherapy (at laparotomy) (1), bowel obstruction (1), age (1) and incorrect diagnosis (gastric carcinoma) (1). The characteristics of the eligible patients are summarised in Table 1. The only imbalance between the two treatment groups involved the extent of original surgery. Patients with <2 cm remaining disease prior to chemotherapy were described as completely debulked, those with between 2 and 5 cm disease at any site were considered partially debulked, and those with >5 cm were assessed as not debulked.

Response to treatment

At 6 months' assessment, 34 patients (45%) were clinically disease-free and a second-look procedure was carried out. The responses obtained with both therapies are shown in Tables 2 and 3, which describe clinical and surgically confirmed responses. These indicate that the rate of clinical objective response to combination therapy was 40% (4 CRs and 12 PRs) and to prednimustine, 36% (3 CRs and 10 PRs). Despite chemotherapy, tumour progression oc-

Table 1. Patient characteristics

		P-HEXUP	Prednimustine	Difference between groups
Mean age		57.6 (SE 8.3)	55.9 (SE 9.0)	
Pathology:	serous	25	20	
	mucinous	5	2	
	endometroid	4	3	NS
	clear cell	0	4	
	adeno/undifferentiated	6	7	
Grade:	1	5	2	
	2	15	15	NS
	3	20	19	
FIGO stage	III	37	31	
	IV	3	5	NS
Performance status (ECOG)	0/1	33	29	
	2/3	6	7	NS
	not recorded	1	0	
Initial surgery	DB <2 cm	11	8	
	PDB 2–5 cm	17	8	$P = 0.063$
	NDB >5 cm	12	20	
	Total	40	36	

DB, debulk; PDB, partial debulk; NDB, not debulked; NS, not significant

Table 2. Clinically evaluated responses

	P-HEXUP	Prednimustine
CR	4	3
PR	12	10
NR	4	3
PD	14	20
NE	6	–
Total	40	36

NE, not evaluable for response

Table 3. True response data in 34 patients[a] who underwent second-look surgery at 6 months

	P-HEXUP	Prednimustine
CR	4	2
PR	10	8
NR/PD	8	2
Total	22	12

[a] Comprising clinical CR patients plus those with no clinically detectable disease following initial surgery who were thus clinically inevaluable

curred in 35% of patients on combination chemotherapy and 56% of patients on prednimustine. In 34 patients who were clinically free of disease at 6 months, a second-look operation was carried out to determine their pathological response status.

Second-look surgery altered the response status from CR to PR for 18 of 22 patients given combination chemotherapy and 10 of 12 patients given prednimustine. The median survival for the group of patients given prednimustine as first-line therapy was 12 months, and for those given combination chemotherapy, 15 months (Fig. 1).

Not surprisingly, the survival patterns were not significantly different ($P = 0.62$; Fig. 2). Initial surgery significantly affected the survival of patients receiving prednimustine but not of those given combination chemotherapy (Figs. 2, 3). The overall median survival for patients with progressive disease was 8 months, for those with PR or NR, 18 months, and that for those with CR has not yet been reached. Five of six surgically CRs as well as the one patient who had a clinically CR (on prednimustine) but did not undergo second-look surgery remain disease-free between 19 and 36 months from the start of chemotherapy (Fig. 4).

Prognostic factors

We examined separately the prognostic significance of pre-treatment, age, pathology, grade of tumour, stage, extent of surgery, performance and serum lactate dehydrogenase (LDH). For patients on combination chemotherapy, only the Eastern Cooperative Oncology Group (ECOG) performance status remained a prognostic determinant in multivariate analysis ($P = 0.0013$) [2]. Age and the extent of surgery were also important, but not after allowing for performance status. For patients treated with prednimustine alone, the extent of surgery was the most significant prognostic variant ($P = 0.0001$), followed by age ($P = 0.0003$).

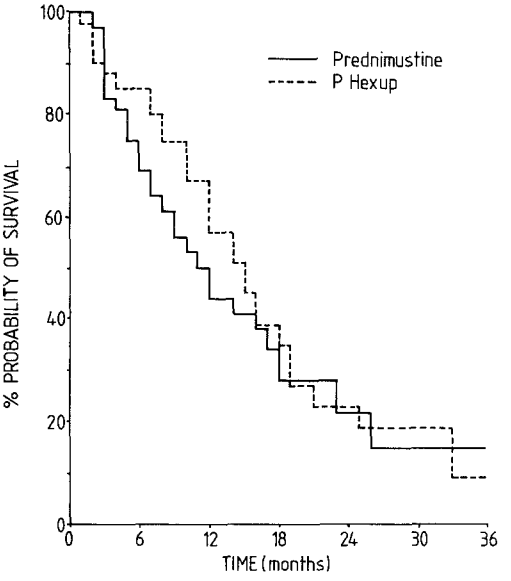

Fig. 1. Survival of patients according to the initial chemotherapy option

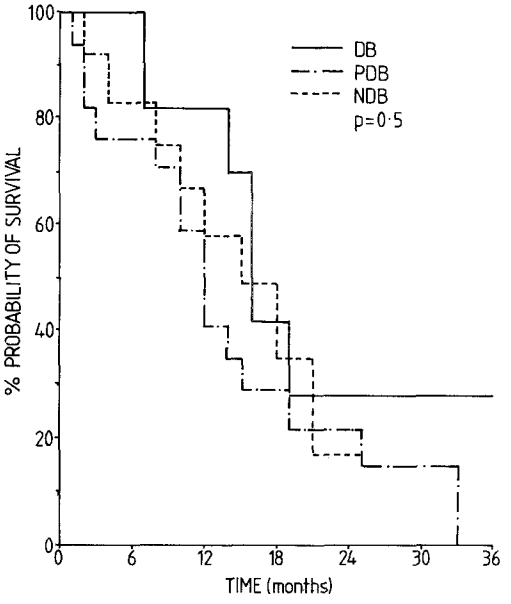

Fig. 2. Initial debulking surgery has no impact on the survival of the P-HEXUP group. *DB*, debulked; maximal remaining tumour, <2 cm. *PDB*, partially debulked; maximal remaining tumour, <5 cm; *NDB*, not debulked

Toxicity of therapy

In all, 65 patients who received a minimum of two courses of first-option drug treatment were evaluable for toxicity (Table 4). The only toxicity of prednimustine therapy was occasional restlessness at night and excessive appetite on days of therapy, presumably mediated by the steroid part of the molecule; haematological and other toxicities were negligible. However, the toxicity of combination chemotherapy was considerable in terms of marked nausea and vomiting for about half of the patients, despite high-dose metoclopramide with or without dexamethasone. The major myelotoxic problem was leucopenia, which necessitated delay of retreatment on 1–4 occasions (mean, 3) for 29

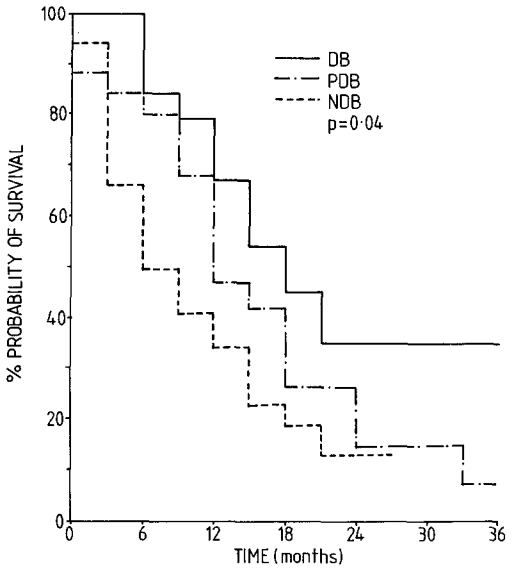

Fig. 3. Initial debulking surgery significantly improves the survival of the prednimustine group

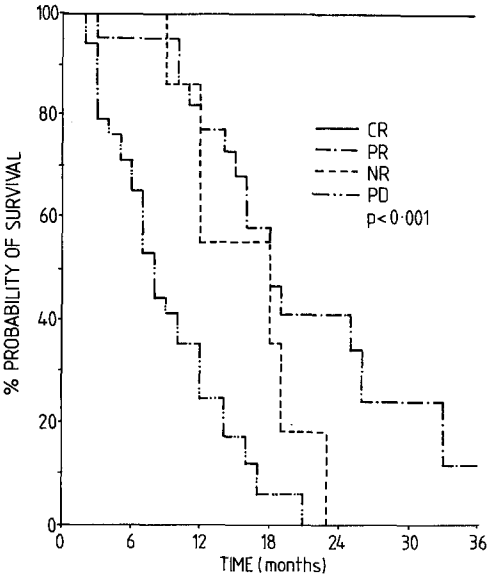

Fig. 4. Complete response at second-look laparotomy correlates with survival

patients on P-HEXUP compared with only 6 patients (mean delay, 1 week) on prednimustine. Thrombocytopenia was rarely significant with either regimen and did not demand treatment delays. On six occasions patients had dose reductions to 50% in cisplatin and 5-fluorouracil to prevent excessive treatment delays.

Salvage therapy

Of 23 prednimustine failures, 17 underwent further chemotherapy; 16 received cisplatin alone at 100 mg/m^2 (13 patients) or in combination (P-HEXUP, 3 patients). Of 13 patients given full-dose cisplatin, 3 responded, 2 of whom were confirmed by second-look laparotomy. These responding patients survived between 9–12 months from the start of second-line therapy, whereas the whole group of prednimustine failures survived for an average of only 5.3 months following the start of salvage therapy. There were no responders in the groups undergoing further chemotherapy after initial prednimustine treatment. Of the 19 P-HEXUP failures, 8 had second-line therapy 4 patients received 100 mg/m^2 cisplatin, 1 received doxorubicin and cyclophosphamide, 2 were given chlorambucil and 1 received the platinum analogue, iproplatin. There were no clinical responses and hence no further laparotomy assessments in this group of patients, who survived for an

Table 4. Toxicity of chemotherapy[a]

	WHO scale	P-HEXUP	Prednimustine	Difference between groups
Nausea/vomiting	0/1	8	25	$P < 0.001$
	2/3	24	8	
Alopecia	0/1	23	31	$P < 0.001$
	2/3+	9	2	
Diarrhoea	0/1	27	33	$P < 0.001$
	2/3	5	0	
Constipation	0/1	27	32	$P < 0.001$
	2/3	5	1	
Haemoglobin	0/1	19	29	$P < 0.001$
	2/3	13	4	
White cell count[b]	0/1	10	26	$P < 0.001$
	2	14	6	
	3	8	1	
Platelet count	0/1	27	32	$P < 0.001$
	2	4	1	
	3	1	0	
Neurotoxicity	Mild (1)	8	0	$P = 0.002$
Renal toxicity	Moderate	11	2	NS

[a] Data represent 32 patients treated by P-HEXUP and 33 treated by prednimustine who completed two or more courses
[b] 25 patients on P-HEXUP vs 6 on prednimustine had treatment delays due to neutropenia (see text)
NS, not significant

average of only 4 months after the start of second-line therapy.

Of 18 patients who partially responded to combination chemotherapy, 11 had salvage therapy for either inevaluable disease following second-look laparotomy (6 patients) or relapsed disease (5 patients). Of the five evaluable (relapsed) patients, one showed further temporary partial regression on high-dose cisplatin. Two inevaluable patients given further post-operative P-HEXUP combination chemotherapy remain disease-free 18 and 30 months after diagnosis. All other evaluable patients failed to respond and, like the remaining four inevaluable patients from this group, subsequently died. Ten patients treated with prednimustine who partially responded to initial therapy (surgical evaluation, 8; clinical, 2) have been retreated with prednimustine (5) or high-dose cisplatin (5). There were no responders to prednimustine, but two of three evaluable patients had a complete clinical response to high-dose platinum. One patient subsequently relapsed and one remains disease-free 18 months after diagnosis. All other patients in these groups subsequently died despite second-line therapy.

Discussion

The present study is the first to demonstrate accurately the promising activity and limited toxicity of prednimustine in ovarian cancer. Many alkylating agents have activity against this disease, but few have been evaluated by surgical [5] and pathological review after treatment. Our comparison of P-HEXUP with prednimustine shows that the remission rate and duration and quality of response are not significantly different for the two regimes. We found that the poorer survival of patients with bulk disease as opposed to that of debulked patients was confined to patients treated with prednimustine alone.

Similar observations were made in patients participating in an ECOG trial that compared melphalan against a combination of cyclophosphamide, doxorubicin, cisplatinum and hexamethylmelamine [14]. In the latter study, the clinical response rates were higher in the combination chemotherapy group, but no advantage was seen for the combination therapy patients (aged <50) who had <2 cm bulk disease at the start of chemotherapy. Again, the overall survival was similar for both arms of the trial.

A variety of combination chemotherapy regimes have been used to treat ovarian cancer, and with increasing dose and drug complexity some regimes have been shown to be superior to HexaCAF in terms of response rate [12]. However, only three studies have claimed that the regime tested positively influenced survival. Young et al. [19] have reported that HexaCAF improved survival compared with melphalan, but this has not been confirmed by other groups [1, 15, 18]. The Swedish cooperative ovarian cancer study group likewise demonstrated improved survival for patients on doxorubicin and melphalan compared with those on melphalan alone [17]. Neijt et al. [11] have reported clear superiority for the CHAP5 regime over HexaCAF. In the latter study, the better survival for the CHAP5 regime was not influenced by the effect of second-line therapy, as all eligible patients were offered salvage therapy including cisplatinum and their overall response rate was about 20%. The authors concluded that the CHAP5 regimen was superior because the dose of cisplatinum was higher than in other combination regimes and was given in nearly full doses over the treatment period. It is possible that our disappointing results with the combination regime are in part at least due to the fact that cisplatinum was given at a low dose (30 mg/m^2 $\times$ 2 per month) in this regime. Young et al. [19] used the same dose of platinum in their modification of the HexaCAF regime incorporating cisplatinum (CHEX-UP). In a series of 51 patients the pathological CR rate was 19%, lower than that observed in the original HexaCAF series, in which there were 13/39 (35%) pathological CRs [12, 20]. Interestingly, a recent randomised study in Italy [4] failed to show a survival advantage for combination chemotherapy over single-agent platinum when the latter was given monthly at 50 mg/m^2.

Among the potential advantages of prednimustine are its lack of myelotoxicity as well as its marked lack of clinical toxicity. The striking lack of clinical or haematological toxicity in our study is in slight contrast to the toxicity reported by Johnsson et al. [8], who described euphoria as a significant problem in his patients. The symptom, ascribed to the steroid content of prednimustine, developed in 22% of the women, who were treated for 2–4 weeks daily at 50 mg/m^2. This problem did not occur in our patients, presumably due to the different scheduling. Thus, prednimustine is an attractive compound for evaluation with other cytotoxic drugs that allows the latter to be given at full or nearly full doses. This may be of particular importance in the design of chemotherapeutic regimens involving second-generation drugs derived from cisplatinum that, although lacking the nephrotoxicity of the latter, are more myelosuppressive. This myelosuppression has complicated the design of studies involving platinum analogues combined with myelotoxic agents such as standard alkylating or intercalating agents. The identification of a new active alkylating agent with minimal myelotoxicity therefore makes prednimustine a particularly interesting drug for future studies on the treatment of ovarian carcinoma.

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