Eur J Cancer Clin Oncol, Vol. 21, No. 12, pp. 1479–1483, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Sequential Chemotherapy for Advanced Epithelial Ovarian Cancer: Platinum Combination Cytoreduction Followed by Cyclophosphamide Consolidation

FRANK LAWTON,*§ GEORGE BLACKLEDGE,* HILARY BUCKLEY,† RICHARD JOHNSON,‡ KRYSTYNA KELLY§ and DEREK CROWTHER*

For the Manchester Ovarian Cancer Clinical Group.
**Cancer Research Campaign, Department of Medical Oncology and ‡Department of Radiology, Christie Hospital and Holt Radium Institute, Wilmslow Rd., Manchester UK., †Department of Pathology, University of Manchester, Manchester, U.K. and §C.R.C. Clinical Trials Unit, Queen Elizabeth Medical Centre, Edgbaston, Birmingham, U.K.*

Abstract—*Thirty-six women with advanced epithelial ovarian cancer were treated with a combination of cisplatin, vinblastine and bleomycin followed by a consolidation regimen of intravenous cyclophosphamide. There was a* 53% *response rate in previously untreated patients with* 25% *complete clinical remissions. Sixteen per cent of previously untreated patients remain in a complete clinical remission of* > 3 yr *duration. In a multivariate analysis bulk tumor residuum was not a significant adverse factor in terms of survival, suggesting that intensive chemical cytoreduction followed by non-cross-resistant consolidation may overcome such prognostic variables.*

INTRODUCTION

THERE is continuing clinical evaluation of combination chemotherapy regimens in the management of epithelial ovarian cancer. Response rates of 80% and greater are frequently reported with the use of cisplatin-containing combinations. Nevertheless, these encouraging response rates may not be translated into long-term survival [1, 2] and frequently the curative potential of these highly active regimes is only seen in those patients with favourable prognostic factors, especially small residual tumour burden [3, 4].

Using the most intensive treatment protocols, improved survival may only be achieved at the expense of considerable side-effects and cumulative toxicity may result in the premature discontinuation of therapy in a large number of cases, life-threatening toxicity or treatment-associated death [5, 6].

Some studies have failed to confirm the superiority of combination regimes over single-agent therapy but emphasise the toxicity of the multi-drug regimens [7, 8].

Clearly, reduction of toxicity is of importance if present drug combinations are to be used optimally. Some data have suggested that alternating or sequencing a number of drugs in combination can reduce toxicity while maintaining high cytotoxic activity [9, 10]. Such regimens are in keeping with the Goldie Coldman hypothesis, which suggests that as many active drugs as possible should be given early in the treatment of the disease whilst the number of spontaneous drug-resistant cell mutations is at a minimum [11]. Regimens of this type may also reduce toxicity since the total dose of each individual agent may be reduced.

In view of this hypothesis, we have studied patients with advanced epithelial ovarian cancer using a protocol involving sequential chemotherapy given at a time when spontaneous resistance may not have developed.

MATERIALS AND METHODS

Thirty-six women with biopsy-proven epithelial ovarian cancer were entered into the study. Patient characteristics and primary surgery undertaken are shown in Table 1. All patients had advanced disease (F.I.G.O. stage IIb residual III or IV). Twenty-nine of the patients had had no previous cytotoxic treatment and seven had failed single-alkylating agent therapy.

Recommended surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy and infra-colic omentectomy, with removal of all macroscopic tumour. Accurate staging of the disease was carried out by inspection of the whole

Accepted 26 July 1985.

peritoneal cavity, cytological examination of ascites or peritoneal washings together with histological examination of multiple peritoneal biopsies or any other suspicious area. Pathology was reviewed centrally by one of us (H.B.). In addition, the bulk of residual disease was recorded, patients being regarded as having either clinically evaluable disease or minimal residual (and therefore clinically inevaluable) disease.

After operation, patients were referred to the Department of Medical Oncology at Christie Hospital. Before chemotherapy commenced the following investigations were carried out: full blood count, biochemical profile, liver and renal function tests and chest X-ray. Thirty patients had computerised tomography of the abdomen and pelvis. All radiographic examinations were reported by the same clinician (R.J.J.).

Treatment regimen (*see Table* 2)

Patients received cisplatin (100 mg/m^2) as a short infusion over 20 min following 24 hr prehydration with 3 l normal saline. Vinblastine 6 mg/m^2 and bleomycin 15 mg were administered immediately after the platinum infusion through the rubber bung of the giving set. Intravenous hydration was continued for another 24 hr and an adequate diuresis of at least 100 ml/hr was maintained with a 20 mg bolus injection of frusemide if necessary. The platinum combination was repeated at 3-weekly intervals to a total of three cycles when a clinical and radiographic reassessment was made.

Responding patients and those with no evaluable disease who had not shown disease progression then entered the consolidation phase of therapy: i.v. cyclophosphamide 1 g/m^2 3-weekly on five

Table 1. *Patient characteristics*

Total = 36 Age (yr): Range 25–66, Median 56

Menopausal status: Pre, 8, Post, 28

Histology		Grade	
Serous	12	Well-differentiated	7
Mucinous	4	Moderate	10
Endometroid	4	Poor	12
Mesonephroid	4	Unspecified	7
Undifferentiated	4		
Unspecified	8		
Stage (FIGO)		Previous treatment	
IIb (residual)	1	(alkylating agent)	7
III	23		
IV	12		
Primary surgery			
TAH and BSO with omentectomy	12		
Bilateral salpingo-oophorectomy only	9		
Biopsy only	15		
Post-surgical status			
No remaining tumour > 2 cm	12		
Bulk disease (> 2 cm)	24		

Table 2. *Treatment regimen*

Cisplatin 100 mg/m^2 i.v.		×			×			×								
Vinblastine 6 mg/m^2 i.v.		×			×			×								
Bleomycin 15 mg i.v.		×	×	×	×	×	×	×	×	×						
Cyclophosphamide 1 g/m^2 i.v.											×	×	×	×	×	
Clinical assessment	×									×						×
Weeks		1	2	3	4	5	6	7	8	9	12	15	18	21	24	27

occasions. Clinical restaging was then repeated. In patients with no evidence of disease a follow-up only policy was adopted. Patients with residual disease were further treated with second-line regimens when they became symptomatic.

Response assessment and toxicity

Standard WHO criteria were used to assess clinical response. In patients with no evaluable disease the progression-free interval was calculated from the start of chemotherapy to the date of clinical disease progression.

Toxicity was assessed using WHO criteria [12]. If toxicity necessitated treatment modification then the time between courses was increased rather than the dose decreased.

RESULTS

All patients have been followed up for a minimum of 42 months or to death. Median overall survival is 16.5 months. The overall survival curve is shown in Fig. 1. Median time to disease progression for previously untreated patients is 12 months.

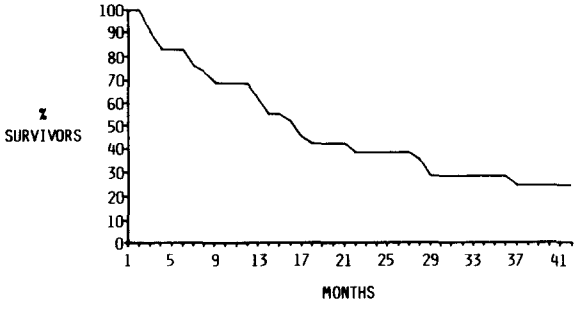

Fig. 1. Overall survival.

Patients with clinically evaluable disease (n = 24)

There were four complete and five partial remissions amongst the 17 previously untreated patients in this group, giving a response rate of 53%, with a clinical complete response rate of 25%. A further four of the seven previously treated patients obtained a partial response.

Of the 13 responses, 11 were seen during the platinum phase of treatment. Two further responses, both complete, occurred during the cyclophosphamide phase.

The median duration of complete remission was 17 months, median survival 14 months. Three patients remain in complete clinical remission at 28, 29 and 30 months.

Patients with minimal residual disease (n = 12)

Median progression free interval was 13.5 months, median survival 28 months. Four patients remain alive without clinical evidence of disease at 29, 40, 40 and 44 months. A fifth patient relapsed at 27 months but remains alive at 35 months (see Fig. 2).

Toxicity (see Table 3)

Only 13 of the planned 108 cisplatin courses were omitted. Four courses were omitted because of the early disease-related death of two patients after only one course of treatment. Nine patients received only two courses (five nausea and vomiting, one electrolyte disturbance, two tinnitus and one disease progression); the cyclophosphamide phase of treatment was therefore commenced in all of these patients. In one further patient the final platinum cycle was delayed by 1 week because of prolonged nausea and malaise.

Thirty-four patients were therefore eligible to commence the cyclophosphamide phase of treatment. Sixteen patients completed the full course without delay or omission of cycles and nine suffered delays of 1 week because of persistant vomiting (three cases) or marrow depression (six cases). Progressive disease caused the early discontinuation of treatment in another nine patients.

Nausea and vomiting was universal. In most cases this lasted for between 12 and 36 hr following cisplatin administration. In eight cases vomiting was so severe that cytotoxic therapy was modified or discontinued. All these patients responded rapidly to parenteral rehydration. Myelotoxicity was generally not a problem. Only five patients had greater than WHO grade II marrow depression and required blood transfusion. There was only one episode of septicaemia which rapidly responded to antibiotic therapy.

Multivariate analysis

A multivariate analysis of factors affecting survival was carried out on previously untreated patients. In a stepwise analysis the variables were entered according to the increase in log likelihood. Remission status provided the biggest improvement in fit (chi-square = 20.20; P = 0.0000). Disease status (bulk disease or minimal residual disease) was less important and did not produce a

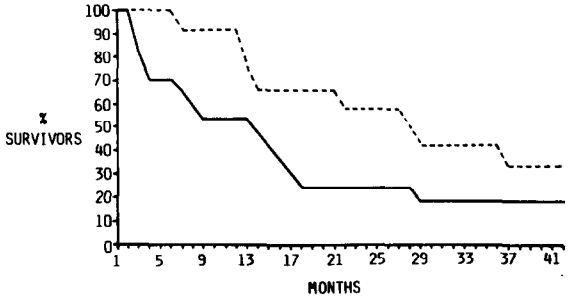

Fig. 2. Survival for patients with minimal (- - - -) and bulk (——) disease residuum.

Table 3. Toxicity (WHO)

	Toxicity grade				
	0	1	2	3	4
Haematological	19	8	4	5	0
Nausea/vomiting	0	0	28	5	3
Renal	24	5	3	4	0
Neurological	28	6	2	0	0

significant improvement in fit of the model, suggesting that any significant difference found using the log-rank test was due to the correlation of disease status with other variables.

DISCUSSION

Most studies of chemotherapy in epithelial ovarian cancer have used a single agent or a number of agents in combination repeated at regular intervals. The potential for development of resistance to therapy and cumulative toxicity is therefore great. The regime reported here has used a platinum-containing combination regime over a relatively short time to induce a remission, with consolidation of the response achieved by an early change of therapy. The optimal number of courses of treatment has never been established but the early sequencing of potentially non-cross-resistant drugs could allow for less toxicity with similar activity to that reported with conventional therapy.

Using this approach in previously untreated patients, a response rate of 53% has been obtained in a group of patients with poor prognostic factors in terms of tumour residuum and grade (Table 1).

Studies using three or four drugs simultaneously have reported higher response rates but with considerably more toxicity, and few of these studies have shown any worthwhile long-term survival benefit over less toxic single-agent therapy [13, 14]. The progression-free interval for our patients with bulky tumour residuum compares favourably with those results reported with the CHAD regimen [3].

The sequencing of agents may be of importance since the platinum combination phase causes a chemical cytoreduction, allowing the second part of the sequence to act at a time when disease residuum is at a minimum. The fact that multivariate analysis failed to show an advantage for patients with minimal residual disease suggests that the adverse significance of bulky disease residuum may be overcome by treating the patient with intensive chemical cytoreduction followed by non-cross-resistant consolidation. Notwithstanding this analysis, it is encouraging that 25% of the patients who had optimum cytoreductive surgery initially are experiencing a > 3-yr disease-free survival. In spite of a minimum of a 42-month follow-up for all patients, it is still too early and the numbers too small to determine whether this represents a significant advance in the treatment of ovarian cancer.

Bleomycin and vinblastine were chosen in this combination because both agents have shown activity in epithelial ovarian cancer [15, 16] and a previous report has demonstrated the activity of the three-drug combination in the disease [17].

It is possible that the drugs used in this study are not those of maximum efficacy in epithelial ovarian cancer but, using the principal of early sequential treatment, further developments could be made with different agents.

This concept of aggressive, short-duration platinum combination chemotherapy followed by single alkylating agent consolidation needs comparison with standard regimens in a randomised trial.

Acknowledgements—We should like to acknowledge the contribution of all members of the Manchester Ovarian Cancer Study Group for their collaboration in this study and the secretarial assistance of Mrs Louise Bennett.

REFERENCES

1. Stehman FB, Ehrlich CE, Einhorn LH, Williams SD, Roth LM, Blessing JA. Long term follow-up and survival in Stage III–IV epithelial ovarian cancer treated with *cis*-dichlorodiamine platinum, adriamycin and cyclophosphamide (PAC). *Proc ASCO* 1983, **2**, 147.
2. Greco FA, Hande KR, Jones HW, Burnett LS. Advanced ovarian cancer: long-term follow up after brief intensive chemotherapy. *Proc ASCO* 1984, **3**, 166.
3. Vogl SE, Pagano M, Kaplan B, Greenwald E, Arseneau J, Bennett B. Cisplatin based combination chemotherapy for advanced ovarian cancer. High overall response rate with

curative potential only in women with small tumour burdens. *Cancer* 1983, **51**, 2024–2030.
4. Greco FA, Julian CG, Richardson RL, Burnett L, Hande KR, Oldham RK. Advanced ovarian carcinoma: brief intensive combination chemotherapy and second-look operation. *Obstet Gynecol* 1981, **58**, 199–205.
5. Neijt JP, ten Bokkel Huinink WW, Van der Burg ME *et al.* Randomised trial comparing two combination chemotherapy regimens (Hexacaf vs CHAP-5) in advanced ovarian carcinoma. *Lancet* 1984, **ii**, 594–600.
6. Budd GT, Webster KD, Reimer RR, Martimbeau P, Livingston RB. Treatment of advanced ovarian cancer with cisplatin, adriamycin and cyclophosphamide: effect of treatment and incidence of intracranial metastases. *J Surg Oncol* 1983, **24**, 192–195.
7. Carmo-Pereira J, Costa FO, Henriques E, Ricardo JA. Advanced ovarian carcinoma: a prospective and randomised clinical trial of cyclophosphamide versus combination cytotoxic chemotherapy (HEXA-CAF). *Cancer* 1981, **48**, 1947–1951.
8. Sturgeon JFG, Fine S, Gospodarowicz MK *et al.* A randomised trial of Melphalan alone versus combination chemotherapy in advanced ovarian cancer. *Proc ASCO* 1982, **1**, 108.
9. Pastmantier MW, Coleman M, Ballard WP, Silver RT. HAC–cyclophosphamide treatment of ovarian carcinoma: alternating-intensification chemotherapy. *Proc ASCO* 1984, **3**, 173.
10. Griffin T, Cederbaum A, Hunter R *et al.* Alternating combination chemotherapy of advanced ovarian cancer. *Proc ASCO* 1983, **3**, 154.
11. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumours to their spontaneous mutation rate. *Cancer Treat Rep* 1979, **63**, 1727–1733.
12. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO Offset Publications, No. 8, 1979.
13. Williams CJ, Mead GM, Green JA *et al.* A randomised study of cisplatin, adriamycin and cyclophosphamide (PACe) versus chlorambucil in Stage III and IV ovarian carcinoma. *Proc ASCO* 1983, **2**, 156.
14. Vogl SE, Kaplan B, Pagano M. Diamminedichloroplatinum (D) based combination chemotherapy (CT) is superior to melphalan (M) for advanced ovarian cancer (OVCa) when age < 50 and tumour diameter > 2 cm. *Proc ASCO* 1982, **1**, 119.
15. Blackledge G, Lawton F, Buckley H, Crowther D. Phase II evaluation of bleomycin in patients with advanced epithelial ovarian cancer. *Cancer Treat Rep* 1984, **68**, 549–550.
16. Salmon SE, Hamburger AW, Soehnlen B, Durie BGM, Alberts DS, Moon TE. Quantitation of differential sensitivity of human-tumour stem cells to anticancer drugs. *N Engl J Med* 1978, **298**, 1321–1327.
17. Ehrlich CE, Stehman FB, Williams SD. Evaluation of vinblastine (VBL), bleomycin (BLEO) and *cis*platinum (CPDD) as a second trial therapy in patients with recurrent ovarian carcinoma. *Proc ASCO* 1982, **1**, 111.