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Speed of Response to Platinum-based Chemotherapy: Implications for the Management of Epithelial Ovarian Cancer

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Abstract—*Seventy-nine patients with evaluable epithelial ovarian cancer following primary laparotomy and treated with one of three primary* cis*-platinum-containing regimens were studied to determine the rate at which clinical cytoreduction occurred and whether a rapid response to treatment was of prognostic signifiance by improving progression free interval (PFI) or survival.*

A rapid response to treatment improved PFI in patients treated with single agent cis*-platinum* (P = 0.04) *and increased survival in patients treated with a sequential* cis*-platinum based combination regimen* (P = 0.03). *The rate of cytoreduction was not a significant variable, however, in a multiple regression analysis of prognostic factors. Over* 75% *of all clinical responses, regardless of the regimen, had begun by the completion of the third course of chemotherapy. We conclude that response to active chemotherapy is a rapid phenomenon in ovarian cancer and this has important implications in both the decision to change drug therapy and the timing of further surgical effort.*

INTRODUCTION

CHEMOTHERAPY has a major role in the management of epithelial ovarian cancer since most patients present with late stage disease which cannot be completely surgically excised [1]. Although the role of chemotherapy in such instances is generally accepted, optimum regimens have not been defined. Combination regimens, especially those containing *cis*-platinum, have produced higher response rates than those generally seen with single drug regimens and randomized studies have shown that this superior activity can be translated into improved median survival, but whether this leads to an improved curative potential remains controversial [2–4].

Clinical observation has suggested that not only are response rates superior when combination regimens are used, but that cytoreduction occurs more rapidly: that is, the interval between the start of chemotherapy and the achievement of a clinical response is shorter. It might be postulated that this more rapid cytoreduction leads to the improved median survival associated with the use of combination regimens.

In this study we have recorded how quickly tumour reduction occured in 79 patients treated with one of three first-line *cis*-platinum-based chemotherapy regimens. The possible benefit to the patient of a more rapid reduction of bulk disease has been evaluated by assessing its effect on progression-free interval and survival.

PATIENTS AND METHODS

The case records of 129 patients, all with biopsy-proven epithelial ovarian cancer, FIGO stage III or IV and who had clinically evaluable disease following suboptimal primary surgery, were studied. Seventy-nine of these patients gained at least a partial response to subsequent chemotherapy as defined by World Health Organization criteria and it is this group that underwent further study.

All patients were treated with one of three primary chemotherapy regimens: single agent *cis*-platinum (DDP), a sequential platinum-containing combination regimen (PVB-C) or an alternating five drug platinum regimen (CP-ABC). Details of the three regimens are given in Table 1. All cycles

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Table 1. Treatment regimens

DDP	*cis*-platinum 100 mg/m²	q 3 weeks	× 5 courses
PVB-C	*cis*-platinum 100 mg/m²		
	Vinblastine 6 mg/m²	q 3 weeks	× 3 courses
	Bleomycin 15 mg		
	followed by		
	Cyclophosphamide 1 g/m²	q 3 weeks	× 5 courses
CP-ABC	*cis*-platinum 75 mg/m²		
	Cyclophosphamide 750 mg/m²		× 3 courses
	alterating 3 weekly with		
	Adriamycin 50 mg/m²		
	Bleomycin 15 mg		× 3 courses
	Chlorambucil 6 mg/m² oral, daily × 7		

were repeated at 3-weekly intervals. The regimens reflect treatment protocols under study by the authors over the past 6 years and have been previously reported [5–7].

Response criteria

Response was assessed using World Health Organization criteria [8]. In terms of this study a clinical response was documented if there was at least a 50% decrease in the product of two perpendicular tumour diameters measured by two observations not less than 4 weeks apart. All patients were jointly examined by a gynaecologist (F.G.L.) and a medical oncologist (G.B.) every 3 weeks throughout the treatment period in order to document the response to chemotherapy. Where appropriate, for instance for patients with small volume clinical residual disease, ultrasound or C.T. scans were used to confirm the clinical response.

Progression free interval (PFI) was defined as the period from the time the maximum clinical response was obtained to the time of disease relapse. The time to response was the interval from the start of chemotherapy to the time that the first clinical response was recorded. In those patients where a partial remission was subsequently translated into a complete remission, the time to maximum response was also recorded.

Other patient and tumour characteristics which may affect progression free interval—age, FIGO stage and histology and grade of the tumour—were obtained from the patients' records. There was review of all histological specimens by one of two gynaecological histopathologists. Patient characteristics by treatment regimen are listed in Table 2.

Data were stored on a Systime 8730 minicomputer at the West Midlands Cancer Research Campaign Trials Unit and analysed using the BMDP statistical software package.

Table 2. Patient characteristics by treatment regimen

	DDP	PVB-C	CP-ABC
Response rate	62%	57%	72%
Total No. of patients	74	34	21
No. of patients responding	46	18	15
No. with CR	27	5	5
Age			
< 50 years	12	5	1
> 50 years	34	13	14
FIGO stage			
III	39	13	10
IV	7	5	5
Histology			
serous	27	10	10
mucinous	5	3	1
endometroid	8	2	0
anaplastic	6	1	3
mesonephroid	0	2	1
Grade			
well	7	3	2
moderate	17	7	6
poor	20	8	6
not known	2	0	1

RESULTS

Progression free interval and survival

The median time to disease progression for the three treatment regimens were 7 months (PVB-C), 11 months (DDP) and 11.3 months (CP-ABC). These intervals are not statistically significant ($P = 0.07$). Median survival time are 14 months, 17 months and 21 months ($P = 0.12$).

Time to response

The median time to first clinical response were 6, 6 and 9 weeks for the PVB-C, DDP and CP-ABC regimens, respectively. The corresponding median times to maximum response were 6.2, 7.6 and 10 weeks.

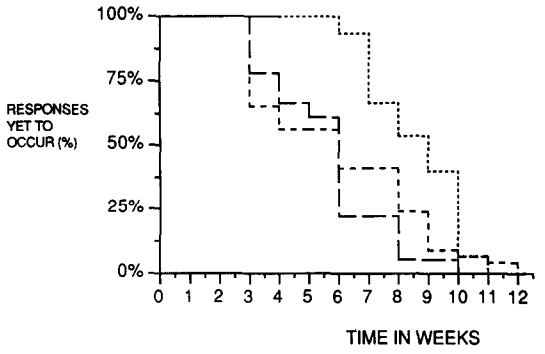

Fig. 1. Time to first response by treatment regimen. DDP – — – —; PVB-C — — —; CP-ABC -----.

If response time is measured in terms of completed courses of chemotherapy, over 75% of all ultimate responses had been recorded by the end of the third course and no additional responses were gained after the completion of four courses of any of the regimens. The rate at which these first responses were recorded is shown in Fig. 1.

Factors influencing progression free interval (PFI) and survival

Analysis by treatment regimen showed that the major influence on progression free interval and survival was the degree of clinical response obtained.

A complete clinical response was associated with a superior PFI and survival compared with a partial response. There were no other variables whose influence reached statistical significance for all three regimens for either PFI or survival. However, progression free interval was improved for those patients who responded more rapidly to single agent *cis*-platinum and there was improved survival for those patients responding more rapidly to the PVB-C regimen. Prognostic factors by treatment regimen are listed in Table 3.

Table 3. Prognostic variable for PFI and survival by regimen

Prognostic variable	Regimen DDP	PVB-C	CP-ABC
For progression free interval			
Age	N.S.	N.S.	N.S.
Stage	N.S.	N.S.	N.S.
Histology	N.S.	N.S.	0.0001
Grade	N.S.	N.S.	0.0005
Clinical response obtained	0.0004	0.004	0.0066
Time to first response	N.S.	N.S.	N.S.
Time to maximum response	0.04	N.S.	N.S.
For survival			
Age	N.S.	N.S.	N.S.
Stage	N.S.	N.S.	N.S.
Histology	N.S.	N.S.	N.S.
Grade	N.S.	N.S.	N.S.
Clinical response obtained	0.0004	0.0001	0.005
Time to first response	N.S.	N.S.	N.S.
Time to maximum response	N.S.	0.03	N.S.

Figures refer to *P* values calculated using the log rank test. N.S.: not significant.

DISCUSSION

In this study it was not our intention to compare the efficacy of the three regimens in any way and in a retrospective analysis such as this, where important prognostic variables may not be comparable between treatment groups, such a conclusion would be meaningless. We have reduced interobserver error to a minimum by stipulating that all patients were examined at 3-weekly intervals by two clinicians—a gynaecologist and a medical oncologist.

This study population is obviously biased to some extent since all patients in this report had sub-optimal primary surgery. Also the constraint that we could only study responding patients rather than the whole population treated by a particular regimen means that patients with a good prognosis would automatically be selected.

However, since all patients were treated with *cis*-platinum at a cumulative dose of between 180 and 500 mg/m^2 and the groups were well balanced for several important prognostic variables, we feel that this factor does not detract from our conclusion that epithelial ovarian cancer responds rapidly to chemotherapy. Over 75% of responses had occurred by the completion of three courses of any of the regimens we examined.

This study has suggested that the speed at which the clinical response to single agent *cis*-platinum occurs may be significant in terms of increasing progression free interval. Since this was not an important factor in the PVB-C or CP-ABC regimens it might be concluded that the addition of other active agents to a *cis*-platinum regimen can allow a reduction in the cumulative dose of *cis*-platinum, in this case from 500 to 225–300 mg/m^2, without prejudicing either the response rate or the rate at which clinical cytoreduction occurs. Such a reduction may have important implications regarding cumulative *cis*-platinum toxicity, but conclusions as to whether such a dose reduction would affect the duration of response require prospective study.

The superior median survival seen in those patients who responded rapidly to PVB-C may be an indication that it is the three *cis*-platinum-containing courses in the regimen which are of prime importance in debulking tumour, sequential single agent cyclophosphamide having little activity against ovarian cancer which is resistant to *cis*-platinum.

Our experience agrees with other reports on the time taken for ovarian cancer to respond to

chemotherapy [9, 10]. Ehrlich *et al.* reported that the 'mean interval to response' for two platinum combination regimens was about 8.5 weeks and Belinson *et al.* found that 77% of ultimate responses had occured within three courses of CAP chemotherapy.

The observation that about 75% of all clinical responses had begun by the completion of three courses of chemotherapy may be of clinical significance in two aspects in the management of ovarian cancer.

The first would suggest that since all responses will have occurred within four courses of chemotherapy it is illogical to continue the same regimen for longer than that in non-responding patients in the expectation of a response. The decision to change treatment in non-responding patients by the third or fourth course of chemotherapy will reduce cumulative toxicity and may theoretically reduce the risk of a clone of resistant cells developing in accordance with the Goldie–Coldman hypothesis [11].

The second aspect concerns the timing of secondary surgery in a combined modality approach to the management of advanced epithelial ovarian cancer. A recent paper concluded that 'second effort' surgical resection of previously inoperable disease was unlikely to benefit the patient if such intervention was attempted after 6 months of combination chemotherapy [12]. Our data would suggest that the decision to attempt further resection should be taken much earlier since it will be apparent within three or four courses of chemotherapy, that is after about 3 months of treatment, whether any significant cytoreduction will occur.

Greco *et al.* [13] concluded that a brief and intensive course of combination chemotherapy was capable of producing marked cytoreduction in most patients and that further surgery should, therefore, be planned after a short interval.

That this approach is feasible and may have therapeutic benefits has been shown by reports from three groups including our own. Neijt *et al.* [14] showed that patients who had undergone successful 'intervention debulking surgery' as soon as cytoreduction made the attempt feasible had a progression free interval approaching that of patients who had undergone optimal primary surgery. Parker *et al.* [15] carried out further surgery after only two courses of an alternating *cis*-platinum regimen and anticipated that the median survival for those patients who had been optimally debulked after this early second surgery would approach that of patients who underwent optimal primary resection of disease. A recent study from our own group [16] has shown that a combination of primary surgery, three courses of cisplatin-based combination chemotherapy and early secondary surgical debulking (at a mean time of 14 weeks from primary laparotomy) can result in more than 70% of patients with advanced ovarian cancer having less than 2 cm disease residuum.

These data would suggest that the decision to attempt further surgery can be taken after completion of only three to four courses of chemotherapy, that is at an interval of between 9 and 12 weeks from the start of treatment.

Clinicians should be aware that epithelial ovarian cancer responds rapidly to chemotherapy and plan the management of patients with the disease appropriately.

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