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A Phase II Study of Carboplatin in Metastatic Transitional Cell Carcinoma of the Bladder

(A report of the Medical Research Council Working Party on Urological Cancer, Subgroup in Advanced Bladder Cancer*)

Abstract—*In view of the activity of Cisplatin in bladder cancer a multicentre study of its less toxic analogue Carboplatin was carried out in 48 patients with metastatic transitional cell carcinoma, of whom 30 had received no previous cytotoxic chemotherapy. No complete remissions and only 3 partial responses were observed, suggesting that Carboplatin has only minimal activity in this disease.*

INTRODUCTION

CISPLATIN is widely used in the treatment of metastatic bladder cancer and is recognised to be one of the most active agents in this disease with an overall response rate of 30% (95% confidence limits 25–35%) [1, 2]. However, Cisplatin is a toxic drug causing renal impairment, high frequency hearing loss, severe emesis and peripheral neuropathy [3]. The impairment of renal function caused by Cisplatin is a particular problem in the treatment of bladder cancer where pre-existing obstructive uropathy is common.

Carboplatin (*cis*-diammine-1, 1-cyclobutanedicarboxylate platinum II) also known as JM8 or CBDCA is an analogue of Cisplatin which has been evaluated in several centres and appears to have activity similar to that of Cisplatin in carcinoma of the ovary [4, 5] and possibly greater activity in small cell lung cancer [6]. In Phase I and Phase II studies little non-haematological toxicity has been observed and, in particular, no substantial nephrotoxicity has been reported [7]. Moreover, Carboplatin may be administered to patients with poor renal function without inducing any further impairment [8]. The dose limiting toxicity of Carboplatin is haematological with thrombocytopenia dominating, although leucopenia also occurs.

Carboplatin is mostly excreted unchanged in the urine [9]. Renal impairment leads to slower excretion and a higher area under the plasma concentration vs. time curve thus requiring dose reduction to prevent excessive myelo-suppression [8, 9]. The lack of nephrotoxicity of Carboplatin and its urinary excretion made it an attractive agent for evaluation in transitional cell carcinoma.

MATERIALS AND METHODS

Treatment

Carboplatin was administered as a 1 hr infusion in 500 ml 5% dextrose solution. Doses were scaled according to the pre-treatment glomerular filtration rate (GFR) and age as shown in Table 1. Carboplatin was repeated every 4 weeks for 3 cycles. A blood count was obtained 3 weeks after each treatment at the anticipated time of platelet nadir. Subsequent dosage was adjusted as follows. If total platelet nadir was between 50 and 100×10^9/l Carboplatin was reduced by 50 mg/m^2; if between 20 and 50×10^9/l the dose was reduced by 100 mg/m^2. If at the time of the second or third cycle the total white cell count was less than 3.5×10^9/l or platelets less than 120×10^9/l treatment was deferred until recovery above these levels.

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Table 1. Dose modification of carboplatin according to glomerular filtration rate and age

Renal function (% of normal lower limit)	Age < 65 years	Age > 65 years
GFR 60%	400 mg/m²	300 mg/m²
GFR 40–60%	300 mg/m²	200 mg/m²
GFR 25–40%	200 mg/m²	100 mg/m²
GFR 15–25%	100 mg/m²	100 mg/m²

Assessment of response

Responses were documented by clinical measurement, ultrasonography, radiography or CT scanning as appropriate. Response was assessed after 3 cycles of treatment, i.e. 12 weeks following commencement of treatment. Those patients showing complete or partial remission received a further cycle of Carboplatin and were re-assessed 4 weeks later. Further treatment with Carboplatin was at the discretion of the investigator. All claimed responses were subjected to independent, clinical, radiological and pathological review and were categorised according to W.H.O. criteria [10].

RESULTS

Patients

Fifty-five patients, all with metastatic transition cell carcinoma, were recruited to the study, but 7 were ineligible and excluded from analysis: 4 because of inadequate performance status, 2 because the diagnosis of transitional cell carcinoma was not confirmed and 1 patient had an inadequate marker lesion. The remaining 48 patients are reported here.

The mean age was 62 years (range 37–79), 40 were male and 8 female. Renal function varied considerably: GFR was > 60 ml/min in 34 patients; 40–60 in 8 patients; 25–40 in 4 patients, and 15–25 in 2 patients. Twenty of the 48 patients received the full initial dose of 400 mg/m² of Carboplatin; in the other 28 patients, the dose was reduced according to protocol. Six received 350 mg/m², 12 received 300 mg/m², 6 received 200 mg/m² and 4 received 100 mg/m². Eleven patients had received prior chemotherapy to metastatic lesion(s); 5 patients had received radio-therapy to metastases but not to their indicator lesion(s). Seven other patients had received systemic chemotherapy during the treatment of their primary bladder cancer before the appearance of metastases. Various cytotoxic agents had been used but only 2 patients had been treated with Cisplatin.

Eighty-two indicator lesions were recorded in the 48 eligible patients: 29 lesions were lung metastases, 38 lymph node metastases and the remainder were liver, pelvic or skin metastases.

Table 2. Total white cell and platelet counts during treatment with carboplatin

White cell count	Cycle 1 WK3	Cycle 1 WK4	Cycle 2 WK3	Cycle 2 WK4	Cycle 3 WK3	Cycle 3 WK4
$<1.0 \times 10^9$/l	0	0	0	0	1	0
$1.1–2.0 \times 10^9$/l	0	1	1	0	0	1
$2.1–3.0 \times 10^9$/l	6	4	5	1	2	4
$> 3.0 \times 10^9$/l	35	38	24	37	21	19
Not done	7	5	11	2	5	5
Not applicable*	0	0	4	5	1	1
Course not given	0	0	3	3	18	18
Platelet Count						
$<25 \times 10^9$/l	0	0	1	0	0	0
$26–50 \times 10^9$/l	3	0	1	1	2	1
$51–100 \times 10^9$/l	3	2	6	1	6	0
$> 100 \times 10^9$/l	33	40	22	36	15	22
Not done	9	6	11	2	6	6
Not applicable*	0	0	4	5	1	1
Course not given	0	0	3	3	18	18

*Patients died before 3 or 4 weeks.

Tumour response

Participating clinicians reported 5 partial remissions and 1 complete remission, but after independent review of X-rays and CT scans no complete remissions and only 3 partial responses were confirmed.

The response rate was therefore 6% (3/48) with 90% confidence limits of 1.7 and 15%. Two of the responding patients had received no prior radiotherapy or chemotherapy; the third patient had received intravenous Methotrexate 1 month before entry to the study.

Toxicity

Thirty patients completed 3 cycles of Carboplatin; three patients withdrew prematurely after the first cycle and 15 after the second dose of Carboplatin. Of these 18 withdrawals 3 were due to treatment toxicity, 10 because of tumour progression, 4 patients died of their tumour and 1 patient of myocardial infarction or pulmonary embolism. Of the 3 patients withdrawn because of treatment toxicity 2 had severe nausea and vomiting and 1 had mild nausea and vomiting with a metallic taste associated with anorexia.

The most frequent side-effects encountered were myelosuppression, nausea and vomiting. The distribution of total white cell count and platelet counts at weeks 3 and 4 is shown in Table 2, and the number of courses delayed for myelosuppression is shown in Table 3. Eight patients experienced severe nausea and vomiting of whom

Table 3. Delay in administration of carboplatin due to myelosuppression

	Days delay				
	0	1–7	> 7	Not known	Not applicable
2nd cycle	15	25	4	1	3
3rd cycle	9	18	2	1	18

2 withdrew from treatment. Thirty-three experienced nausea and vomiting graded as mild to moderate. Only 7 patients did not experience these symptoms during study. Two patients suffered profound loss of concentration and vacant feelings which became worse with each treatment and went away before the next cycle.

There was no evidence of renal impairment caused by Carboplatin during this study. Three patients died of renal failure, but the responsible clinician in each case judged that this was due to tumour progression in the pelvis causing bilateral ureteric obstruction and consequent renal failure.

DISCUSSION

The response rate seen in this group of patients was disappointing and less than that reported for Cisplatin. It seems unlikely that previous treatment could have prejudiced this result because the group included 30 patients who had not received any chemotherapy previously and 37 who had not received prior chemotherapy for their indicator lesion(s). A recent study of the activity of Carboplatin in bladder xenografts has also demonstrated that Carboplatin is less effective than Cisplatin if given as a bolus dose, although its therapeutic efficacy is enhanced by the use of a fractionated dose schedule [11]. It is of interest that a recent paper has reported a response rate for Carboplatin in small cell lung cancer which is higher than that recorded for Cisplatin [12, 13]. This, and the data showing activity of Carboplatin in Cisplatinum resistant ovarian patients [4] suggests that the two drugs may have a different spectrum of anti-tumour activity.

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