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High Dose Carboplatin in The Treatment of Lung Cancer and Mesothelioma: a Phase I Dose Escalation Study

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Abstract—*Sixteen patients with lung cancer or mesothelioma have been treated with escalating doses of carboplatin. Five patients* (10 *courses*) *were given* 800 mg/m^2, *four patients* (*five courses*) 1200 mg/m^2 *and seven patients* (*eight courses*) 1600 mg/m^2. *Myelosuppression was the major toxicity encountered. The median duration of grade* 4 *neutropenia ranged from* 1 *day* (800 mg/m^2) *to* 11 *days* (1600 mg/m^2) *and the median duration of grade* 4 *thrombocytopenia ranged from* 1 *day* (800 mg/m^2) *to* 7 *days* (1600 mg/m^2). *The median fall in haemoglobin* (*Hb*) *ranged from* 2.2 g/l (800 mg/m^2) *to* 3.6 g/l (1600 mg/m^2). *Nephrotoxicity was encountered at all dosages and was in part, though not entirely, dose related.* 2/9 *patients receiving* 800 mg/m^2 *and* 4/6 *of the patients receiving* 1600 mg/m^2 *had a fall in glomerular filtration rate* (*GFR*) > 25% *but* < 50%. 800 mg/m^2 *of carboplatin was well tolerated, the performance status in* 9/10 (90%) *courses being* 0–1 (*ECOG scale*). *At* 1600 mg/m^2 *in* 6/8 (75%) *courses the performance status was* 2–4. *There was one treatment-related death from neutropenia at this dose level. The severity of nausea and vomiting was not dose related but other toxicities including diarrhoea, alopecia, mild neuropathy and ototoxicity and possible CNS toxicity occured at doses of* 1200 mg/m^2 *and over.* 5/7 *patients with small cell lung cancer achieved a complete or partial response to treatment.*

INTRODUCTION

CARBOPLATIN, a cisplatin analogue, has been shown to have good clinical activity against several malignancies including carcinoma of the ovary [1, 2] and small cell lung cancer (SCLC) [3]. In contrast to cisplatin, neuro-, nephro- and ototoxicity rarely occur at conventional dosage (400 mg/m^2) and myelosuppression is dose limiting [4–6]. In recent years high dose chemotherapy with antibiotic and platelet support, and sometimes also with autologous bone marrow rescue, has been shown to be feasible for several drugs when the conventional dose-limiting toxicity is melosuppression [7–10]. We have therefore undertaken a phase I high dose escalation study of carboplatin.

MATERIALS AND METHODS

Patients

Sixteen patients referred to the Lung Unit, Royal Marsden Hospital, London and Surrey were entered into the study. Seven patients had SCLC (five extensive disease, two limited disease), five had non-small cell lung carcinoma (NSCLC) and four pleural mesothelioma. The two patients with limited disease SCLC were given high dose carboplatin (800 mg/m^2) as they refused to accept chemotherapy that would cause significant alopecia. There were eight male and eight female patients, with a median age of 62 years (range 34–71 years). All had histologically confirmed malignancy, an ECOG performance status of 0–2 and clinical or radiological evidence of disease progression. No patient had received any prior chemotherapy or radiotherapy and all patients had a [^{51}Cr]EDTA clearance of > 65 ml/min.

Treatment

Patients receive 1 l. of normal saline i.v. over 8 h before carboplatin administration and subsequently 3 l. of normal saline i.v. over 24 h. Carboplatin (Bristol-Myers International Corp., Brussels, Belgium) was administered i.v. in 500 ml of 5% dextrose over 1 h. All patients received an i.v. antiemetic regimen of lorazepam 1 mg, metoclopra-

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Table 1. *Number of patients treated and courses given at* 800, 1200 *and* 1600 mg/m^2 *carboplatin*

	No. of patients	No. of courses
800 mg/m^2	5	10
1200 mg/m^2	4	5
1600 mg/m^2	7	8
Total	16	23

mide 20 mg and dexamethasone 8 mg at the start of chemotherapy and subsequently 6, 12 and 18 h later.

Patients were treated with escalating doses of 800, 1200 and 1600 mg/m^2 carboplatin. Table 1 shows the number of patients and courses at each dose level. Six patients received more than one course at 4 week intervals but no intra-patient dose escalations were made.

Autologous bone marrow rescue was not carried out and patients were nursed either in the open ward or in a single room but without any special barrier nursing precautions. Broad spectrum i.v. antibiotics were not given prophylactically but only on clinical or bacteriological evidence of infection. Patients whose Hb fell below 9.0 g/l were transfused with packed red cells and platelet transfusions were administered daily while the platelet count was below 20×10^9/l.

Assessment of response and toxicity

Prior to treatment all patients had a full physical examination, and the following investigations: full blood count, plasma urea and electrolytes, serum liver function tests and calcium, chest X-ray, audiogram and measurement of GFR by [^{5}Cr]EDTA clearance. Other investigations including CT scans, isotope bone and liver scans and bone marrow aspirate were carried out as appropriate to document tumour extent.

Patients were assessed daily while on the ward by physical examination and toxicity was also assessed daily using WHO criteria [11]. Full blood counts were done daily during the period of myelosuppression; plasma urea and electrolytes, serum liver function tests and calcium were assessed twice weekly and chest X-rays were done weekly. Four weeks after each course audiograms and [^{51}Cr]EDTA clearances were repeated wherever possible.

Tumour response was defined according to standard criteria: complete response (CR) was defined as the disappearance of all clinical, radiological and biochemical evidence of disease for at least two months; partial response (PR) was defined as a reduction in the product of 2 diameters of measurable disease by at least 50% for at least 1 month [11]. Toxicity was graded according to standard WHO criteria except for nausea and vomiting since all patients received prophylactic antiemetics. This was graded as 1 nausea, 2 less than four episodes of vomiting, 3 more than four episodes of vomiting and 4 intractable vomiting.

All patients gave their informed consent based on their understanding of the experimental nature of this study, and according to the guidelines laid down by the Medical Ethical Committee at The Royal Marsden Hospital. Two patients who were offered high-dose carboplatin treatment declined to enter the study after full discussion.

RESULTS

Toxicity

Myelosuppression was the main toxicity encountered and details are given in Tables 2 and 3. At 800 mg/m^2 grade 4 neutropenia occurred in 5/10 (50%) courses. The median duration of grade 4 neutropenia at this dosage was 1 day (range 0–10). At 1200 and 1600 mg/m^2 all patients suffered grade 4 neutropenia for a median duration of 6 days (range 4–10 days) and 11 days (range 8–14 days), respectively.

The median time to reach grade 4 neutropenia shortened with dose escalation and was 13 days at 800 mg/m^2, 11 days at 1200 mg/m^2 and 9 days at 1600 mg/m^2. Similarly, the median time to reach the neutrophil count nadir shortened as the dose of carboplatin was escalated (Table 2).

At 800 mg/m^2, 5/10 (50%) patients suffered grade 4 thrombocytopenia with a median duration of 1 day (range 0–3 days). At 1200 and 1600 mg/m^2 grade 4 thrombocytopenia occurred in every course: its median duration was 2 days (range 1–3 days) and 7 days (range 3–8 days), respectively. The median time to reach grade 4 thrombocytopenia shortened with dose escalation and was 15 days (range 13–16 days) at 800 mg/m^2, for the five patients who developed grade 4 thrombocytopenia, and 12 days for both 1200 and 1600 mg/m^2 (range 10–16 and 10–12, respectively). However, the time to reach the median day of the platelet nadir was similar for all dosages (Table 3). All patients treated at 1200 and 1600 mg/m^2 received platelet support: the median number of units given per course was 16 (range 8–36) and 22 (range 12–58), respectively. Six out of ten coures at 800 mg/m^2 required platelet transfusion, the median number of units required per course was 6 (range 0–10).

Table 4 shows the degree of anaemia encountered during myelosuppression due to carboplatin. At 800 mg/m^2 the median fall in haemoglobin concentration was 2.2 g/dl (range 1.4–3.7), at 1200 mg/m^2 it was 3.1 g/dl (range 1.9–5.5) and at 1600 mg/

Table 2. Haematological toxicity (neutropenia) of high dose carboplatin

	800 mg/m²	1200 mg/m²	1600 mg/m²
Median nadir* (range)	0.46 (0–1.4)	0.08 (0–0.15)	0 (0)
Day of nadir (range)	16 (11–20)	14 (11–16)	12 (9–13)
Duration $< 0.5 \times 10^9$/l in days (range)	1 (0–10)	6 (4–10)	11 (8–14)

*Neutrophil count $\times 10^9$/l.

Table 3. Haematological toxicity (thrombocytopenia) of high dose carboplatin

	800 mg/m²	1200 mg/m²	1600 mg/m²
Median nadir* (range)	30 (14–73)	17 (4–21)	17 (7–19)
Day of nadir (range)	14 (14 17)	14 (11–17)	13 (10–16)
Duration $< 25 \times 10^9$/l in days (range)	1 (0–3)	2 (1–3)	7 (33–8)

*Platelet count $\times 10^9$/l.

Table 4. Haematological toxicity (anaemia) of high dose carboplatin. Anaemia graded according to WHO criteria

	800 mg/m²	1200 mg/m²	1600 mg/m²
Median fall in Hb g/100 ml (range)	2.2 (1.4–3.7)	3.1 (1.9–5.5)	3.6 (1.9–4.4)
Day of nadir (range)	14 (11–21)	16 (9–25)	17 (13–20)
Grade 1 anaemia (Hb 9.5–10.9 g/100 ml)	6	1	4
Grade 2 anaemia (Hb 8.0–9.4 g/100 ml)	4	4	3
Grade 3 anaemia (Hb 6.5–7.9 g/100 ml)	—	—	1

Table 5. Nephrotoxicity for each course of high dose carboplatin expressed as a percentage fall in GFR. Three patients were not reassessed after treatment

	800 mg/m²	1200 mg/m²	1600 mg/m²
No significant fall in GFR	4	1	2
10–25% fall in GFR	3	—	—
25–50% fall in GFR	2	3	4
> 50% fall in GFR	—	1	—

m² it was 3.6 g/dl (range 1.9–4.4). At 800 mg/m², 6/10 (60%) and 4/10 (40%) courses were associated with WHO grade 1 and 2 anaemia, respectively, at 1200 mg/m², 1/5 (20%) and 4/5 (80%) courses were associated with WHO grade 1 and 2 anaemia, respectively. At 1600 mg/m², 4/8 (50%), 3/8 (37.5%) and 1/8 (12.5%) courses were associated with WHO grade 1, 2 and 3 anaemia, respectively. The duration of anaemia was not evaluable since patiens whose haemoglobin dropped below 9 g/dl received packed red cell transfusions.

Table 5 shows the nephrotoxicity encountered with high dose carboplatin. Twenty out of 23 courses were followed up with a [^{51}Cr]EDTA clearance study. Nine out of 10 courses at 800 mg/m² were evaluable for nephrotoxicity and the results expressed as a percentage fall in GFR per course of treatment. There was no significant reduction in GFR in four (45%) courses, a 10–25% reduction in three (33%), and in two (22%) courses the fall was between 25–50%. At 1200 mg/m², in 1/5 (20%) courses there was no significant fall in GFR in 3 (60%) the fall was between 25 and 50% and in one (20%) the fall was > 50%. At 1600 mg/m², 6/8

Table 6. Subjective toxicity (WHO scale) of high dose carboplatin per course of treatment

		0	1	2	3	4
Peformance status	800 mg/m²	7	2	1		
	1200 mg/m²	2	3			
	1600 mg/m²	1	1	4		2
Nausea/vomiting	800 mg/m²	1	3	2	4	
	1200 mg/m²			4	1	
	1600 mg/m²			7	1	
Infection	800 mg/m²	10				
	1200 mg/m²	2	1	2		
	1600 mg/m²	1	5		1	1
Diarrhoea	800 mg/m²	9	1			
	1200 mg/m²	1	2	2		
	1600 mg/m²	2	2	2	2	
Hair loss	800 mg/m²	8	2			
	1200 mg/m²	3	2			
	1600 mg/m²	4	2		2	
Neuropathy	800 mg/m²	10				
	1200 mg/m²	4	1			
	1600 mg/m²	6	2			
Mucositis	800 mg/m²					
	1200 mg/m²	3		2		
	1600 mg/m²	5	1	2		
Rash	800 mg/m²	8	2			
	1200 mg/m²	5				
	1600 mg/m²	6	2			
Constipation	800 mg/m²	7	3			
	1200 mg/m²	4	1			
	1600 mg/m²	6	2			

courses were evaluable for nephrotoxicity; in two (33%) there was no significant fall in GFR and in four (67%) the fall was between 25 and 50%. Toxicity did not seem to be entirely dose related, nor was it related to the age of the patient or the concomitant administration of aminoglycosides.

Subjective toxicities as defined by WHO criteria are shown in Table 6. The performance status of patients treated with 800 mg/m² remained good, with nausea and vomiting being the main side effects. No patient developed neuropathy or suffered an infection at this dose level and although two patients had minimal (grade 1) hair loss they did not require a wig. At 1600 mg/m², the performance status of patients was very much worse; 6/8 (75%) of the courses were associated with an ECOG performance status of 2 or more and two (25%) of these courses were associated with an ECOG performance status of 4. Severe infections (grade 3–4) were seen in two patients at this dose, one of whom died as a result. In addition, at this dose in 2/8 (25%) of the courses total, but reversible, alopecia developed. This was a delayed effect and appeared about 4 weeks after treatment. At doses of 1200 and 1600 mg/m² some patients complained of diarrhoea and parasthesiae. At 1200 mg/m² grade 2 diarrhoea occurred in 2/5 (40%) courses and at 1600 mg/m² grade 3 diarrhoea occurred in 2/8 (25%) courses. Neuropathy (grade 1) presenting as peripheral paraesthesiae was seen at both higher dose levels in three patients. Malaise lasting 1–7 days occurred in 9/23 courses at all dose levels and its severity was dose related. Three patients complained of a specific 'hangover' effect where the malaise was associated with headache. This effect lasted 5–7 days and only occurred in patients receiving 1200 mg/m² or more of carboplatin.

Objective ototoxicity was seen in three patients (50–60 db loss at 8000 Hz) who receive 1200 and 1600 mg/m² of carboplatin. No long term subjective hearing loss was noted, but in eight courses patients complained of short-term tinnitus lasting 1–10 days and in two patients receiving 1600 mg/m² this was associated with transient subjective hearing loss.

Seven patients received radiotherapy after high dose carboplatin. Five patients received mediastinal irradiation (30–40 gy in 10–20 fractions) and although one patient developed pneumonitis these symptoms subsided after steroid therapy and were no more severe than that seen after conventional

Table 7. Clinical and therapeutic details of patients with SCLC receiving high dose carboplatin (800, 1200, 1600 mg/m^2)

Patients	Stage	Dose (mg/m^2)	No. of courses	RT dose, Gy (fractions)	Response	Survival in days
SA	ED	800	2	40 (20)	PR	347
MC	ED	800	2	—	NC*	257+
LF	ED	800	3	30 (15)	CR	264+
RC	ED	1200	1	30 (15)	PR	145
SS	ED	1600	1	—	NE	14
PR	LD	800	2	30 (15)	PR*	89+
OR	LD	800	1	30 (15)	CR*	199+

ED = extensive disease; LD = limited disease; PR = partial response; CR = complete remission; NC = no change; NE = not evaluable; + = still alive; * = no progression or relapse of disease.

chemotherapy for SCLC. One patient received dorsal spine irradiation (30 Gy in 10 fractions), one patient cranial irradiation (30 Gy in 10 fractions) and one patient irradiation to the supra-adrenal area. There was no evidence of any increased toxicity from radiation in any of these patients. In particular, no skin or oesophageal toxicity was encountered in any of the patients who received radiotherapy.

Response

The overall response rate for patients with SCLC was 5/7 (72%) with two patients (29%) achieving complete remission (Table 7). Of the two patients who failed to respond, one died during treatment but the other continued with stable disease for over 8 months and has as yet not had any further progression of her disease. *Post mortem* examination of the patient who died 14 days after treatment failed to show any viable tumour. The two patients with limited disease are alive and well with no evidence of progression at 199 and 89 days, respectively; one achieved a complete response. The one patient with extensive disease who had a complete remission relapsed after 264 days and the two patients with extensive disease who had partial remissions relapsed after 56 and 105 days, respectively. No response was seen in any of the patients with NSCLC or mesothelioma.

DISCUSSION

This study has demonstrated that the conventional dose of carboplatin (400 mg/m^2) can be escalated at least 4-fold to 1600 mg/m^2. As we anticipated, this dose was associated with severe myelosuppression, but a key feature was its relatively short duration (a median of 11 days neutropenia) making it readily manageable, except in one patient, with standard supportive measures. Autologous bone marrow rescue was not used, and it is most unlikely that this procedure would have been of significant benefit, because the duration of myelosuppression encountered was only slightly longer than the time required for an autologous marrow transfusion to reconstitute [12]. In this respect the pattern of bone marrow recovery for carboplatin resembles that seen with high dose cyclophphamide for which marrow rescue has been shown to be unnecessary [7], and is significantly more rapid than for high dose melphalan or BCNU where rescue enhances peripheral blood count recovery [9, 12].

Bone marrow suppression is not, therefore, dose limiting even at 1600 mg/m^2, but at this dosage several other worrying toxicities reminiscent of the parent compound cisplatin begin to emerge including nephrotoxicity, neurotoxicity and ototoxicity.

Nephrotoxicity is a well recognized complication of cisplatin therapy [13, 14]. It has been suggested that this is related to the presence in the kidney of reactive platinum species [15], the formation of which is favoured by low concentrations of chloride ions. Data from animal studies support this hypothesis and have shown that chloruresis can protect the kidneys from such damage [16, 17]. A similar approach has been adopted in man and i.v. hydration does seem to lessen the severity of cisplatin nephrotoxicity [13, 18, 19]. However, escalating the dose of cisplatin results in a high incidence of nephrotoxicity even when hydration is used [20]. Very high doses (200 mg/m^2) are associated with greater than 30% nephrotoxicity even when given with aggressive saline hydration regimens [21], although perhaps not always [22]; without superhydration the incidence and severity would undoubtedly be much worse. Carboplatin is largely excreted in the urine and it has been suggested that only a small fraction is in the form of reactive platinum [15]. High doses might therefore result in high enough concentrations of these reactive species to cause measurable nephrotoxicity. Rigorous diuresis may reduce the incidence of neophrotoxicity with high dose carboplatin through a simple dilution effect. The precise mechanism of carboplatin

nephrotoxicity and how it might be overcome remains to be studied.

Neurotoxicity in the form of peripheral neuropathy is an important complication of cisplatin therapy and is eventually dose limiting [21, 23]: at 200 mg/m^2 37% of pretreated patients developed grade III neuropathy and 18% of previously untreated patients had difficulty walking [21, 24]. Neurotoxicity is not a problem with carboplatin at conventional dosage and likewise was not seen in this study at 800 mg/m^2. However, its gradual appearance at higher doses suggests an eventual dose–response relationship for this drug, and we would predict that further dose escalations above 1600 mg/m^2 would lead to increasingly severe peripheral neuropathy. A similar pattern appears to emerge for ototoxicity. High frequency hearing loss is a common and at least partly dose-related problem with cisplatin [14, 21]. It does not occur with carboplatin at conventional dosage or here at 800 mg/m^2, but was demonstrated by audiometry in three patients at 1200–1600 mg/m^2. Fortunately this was only associated with transient subjective hearing impairment or tinnitus, but it seems likely that further dose escalations would be associated with more severe and persistent ototoxicity.

The consistent complaints of malaise with headache and a 'hangover' effect at higher doses suggests that some CNS toxicity may also occur with carboplatin. Such symptoms have not been reported with high dose cisplatin; indeed studies in animals and man show that only a very small proportion of an i.v. dose enters the CNS [25, 26]. Recently, it has been demonstrated that in animals the CNS penetration of carboplatin is four times that of cisplatin (Siddik Z.H., personal communication), and measurable amounts of platinum have been found at autopsy in the brain of the patient who died after receiving 1600 mg/m^2 of carboplatin. The extent to which further dose escalation would lead to more severe CNS toxicity is unpredictable from our data, and this would have to be monitored very closely in future studies.

In view of the increasing incidence of ototoxicity, nephrotoxicity and possible CNS toxicity with increasing doses of carboplatin further dose escalations were not undertaken.

In the small number of patients treated, we saw no evidence of activity for high dose carboplatin against NSCLC or mesothelioma; in contrast high dose therapy was highly active in 5/7 patients with SCLC, reflecting the high activity of conventional dose carboplatin against this tumour [3]. The long term role, if any, for very high dose carboplatin in the treatment of SCLC remains to be studied, although it has to be noted that other forms of high dose chemotherapy have not so far suggested a survival benefit for this disease [7, 27, 28]. However, we were impressed that carboplatin at intermediate doses of 800 mg/m^2 was very well tolerated, readily manageable and did not cause distressing alopecia. Short duration treatment at this dosage may have a useful place in the palliative management of patients with SCLC. Finally, high dose carboplatin now merits further study in other sensitive tumours including in particular ovarian carcinoma.

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