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Carboplatin in the treatment of metastatic carcinoid tumours and paraganglioma: a phase II study

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Summary. A total of 13 patients with metastatic carcinoid tumour, paraganglioma, or unclassified "apudoma" were treated with single-agent carboplatin at a dose of 400 mg/m^2 given by intravenous infusion every 4 weeks, on the basis that this new agent shows high activity against small-cell lung cancer that also has "apudoma" characteristics. No objective tumour responses were seen. Overall, 2 patients achieved minor regression, 4/9 (44%) showed a reduction of >50% in urinary 5-HIAA excretion and 8/13 (62%) reported symptomatic improvement. Treatment was well tolerated, with neutropenia and thrombocytopenia being the main toxicities. Carboplatin, like other cytotoxic agents, does not appear to have major activity against these tumours, although further studies in patients with metastatic paraganglioma are warranted.

Introduction

Metastatic carcinoid tumours are not generally responsive to conventional chemotherapy. Carboplatin, a recently developed analogue of cisplatin that lacks the nephro- or neurotoxicity of the parent compound, is highly active in the treatment of small-cell lung cancer [8]. Carcinoid tumours and small-cell lung carcinoma share APUD (amine precursor uptake and decarboxylation) characteristics [7], and we therefore assessed the activity of carboplatin in patients with metastatic carcinoid tumours.

These tumours characteristically have a long natural history; therefore, conservative symptomatic management alone is appropriate in the early stages of metastatic disease. For this reason, patients were entered into this study only when they had progressive symptomatic disease that was no longer controllable by medical treatment including pharmacological blocking agents, such as cyproheptadine, or the mediator of hormone release, somatostatin. Patients with metastatic paraganglioma were also included in this study since these rare tumours are also "apudomas", about which few data have been published on the responsiveness to chemotherapy.

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Patients and methods

Patients. A total of 13 patients with metastatic carcinoid tumour (10), paraganglioma (2) or unclassified "apudoma" (1) were entered into the study. All primary tumours were histologically classified. Metastatic disease was established clinically or by imaging techniques in all patients and confirmed as carcinoid either histologically or on the basis of an elevation in urinary 5-HIAA excretion. Only patients with a WHO performance status of ≤ 2 and a life expectancy of >3 months were entered. Six were men and 7, women; their median age was 53 (range, 29–73) years. Details of the primary disease, metastatic spread, urinary 5-HIAA levels and time from diagnosis are given in Table 1.

Previous therapy for metastatic disease. Three patients had received previous cytotoxic chemotherapy [Adriamycin (patient 9); 5-fluorouracil (5-FU), DTIC, Adriamycin and cyclophosphamide (patient 10); etoposide and Adriamycin (patient 12)]. Two had undergone hepatic arterial embolisation (patients 1,6); one, a therapeutic dose of ^{131}I-MIBG (patient 1); and two, radiotherapy (patients 1,8). Six patients had received no previous antitumour therapy. No patient had received specific antitumour therapy within 6 weeks of starting carboplatin, and none of the patients on pharmacological blocking therapy had their dose changed immediately before or during therapy.

Dose and schedule. Carboplatin was given at a dose of 400 mg/m^2 in 500 ml 5% dextrose as a 1-h infusion that was repeated every 4 weeks. Patients whose WBC nadir fell to $<1 \times 10^9$/l or whose platelet nadir fell to $<75 \times 10^9$/l had their subsequent doses reduced by 25%. Treatment was delayed if the WBC count was $<3 \times 10^9$/l or the platelet count was $<100 \times 10^9$/l.

The dose was adjusted according to renal function as follows: Normal (N)–1.25 N serum creatinine, no dose modification; 1.26N–2.5N, dose reduced to 75% of the total; 2.51N–5N, dose reduced to 50% of the total; >5N, treatment interrupted.

Anti-emetics were given routinely to all patients, with repetition after 6 h to prevent the delayed emesis associated with carboplatin [1]. Carboplatin was continued for as long as patients appeared to obtain symptomatic benefit.

Table 1. Patient characteristics

Age:	29–73 years (median, 53 years)	
Sex:	6 men : 7 women	
Diagnosis:	Carcinoid tumour	10
	(primary site unknown, 4; ileum, 2; bronchus, 2; rectum, 2)	
	Paraganglioma	2
	Pancreatic "Apudoma"	1
Secondary sites:	Liver	12
	Lung	1
	Nodes	3
	Bone	1
	Mesenteric masses	2
	Bone marrow	1
Time from diagnosis:	1–288 months (median, 29 months)	
Urinary 5HIAA (μmol/24 h):	177–2,440 (median, 292)	
	(elevated in 9/10 with carcinoid tumour)	

Table 2. Response of patients to carboplatin treatment

Tumour	Patient	Courses (*n*)	5-HIAA (μmol/24 h)	Marker	Response
Paraganglioma:	1	5	NS	CT	MR
	2	1	NS	CT	PD
Carcinoid:					
	3	3	1,210-182-509	CT	NC
	4	4	1,332-311-1,930	CT	NC
	5	1	177	CT	PD
	6	3	232-208	CT	NC
	7	6	1,681-800	CT	NC
	8	5	292-238	NMR	NC
	9	5	115-105	CT	MR
	10	2	NS	CT	PD
	11	3	2,440-1,845	CT	PD
	12	4	195-18	CT	PD
Unclassified "apudoma":					
	13	3	NS	CT	NC

NS, nonsecreting; CT, computerised tomography; NMR, nuclear magnetic resonance; MR, measurable reduction in tumour bulk; PD, progressive disease; NC, no change

Staging and investigations. Prior to treatment all patients underwent a full clinical examination, a full peripheral blood count, determination of plasma urea and electrolyte values and serum liver-function tests. The 24-h urinary 5-HIAA excretion was assessed in patients with carcinoid tumours. Computerised tomographic (CT) scanning, ultrasound or nuclear magnetic resonance (NMR) examinations were used to assess tumour masses, and other investigations, including isotopic bone scans, were carried out where clinically appropriate. Patients were reassessed by basic investigation prior to each course of treatment, and CT scans/ultrasound examinations were repeated after every two courses.

Response and symptom assessment. Objective response was defined according to standard criteria as follows: complete response, the disappearance of all clinical, radiological and biochemical evidence of disease for a period of at least 2 months; partial response, the reduction in the product of two perpendicular diameters of measurable disease by at least 50% for at least 1 month. Tumour-related symptoms were documented prior to each course of treatment.

Results

Response

No patient achieved a complete or partial objective tumour response according to standard criteria (Table 2). Two patients achieved a measurable reduction in tumour bulk but by less than the 50% necessary to represent a partial response (one carcinoid, patient 9; one paraganglioma, patient 1).

However, 4 of the 9 patients with raised urinary 5-HIAA excretion showed significant decreases (>50%) after their first course of treatment, as follows: from 1,210 to 182 μmol/24 h (patient 3), from 1,332 to 311 μmol/24 h (patient 4), from 1,681 to 800 μmol/24 h (patient 7) and from 195 to 18 μmol/24 h (patient 12). All four reported an improvement in symptoms (anorexia, pain, flushing/diarrhoea and lethargy, respectively). Another 4 patients also noticed an improvement in symptoms [total, 8/13 (62%)]: patient 1 could stop diuretic therapy, which had been commenced to treat her tumour-associated, high-output cardiac failure. She remained symptom-free for 9 months. Patient 8, who had bony metastases associated with a bronchial carcinoid, could completely discontinue morphine therapy after one course of treatment, and this improvement persists 1 year later. Other patients reported short-term improvements in pain (patients 13) and carcinoid symptoms (patient 11).

Toxicity

Carboplatin was well tolerated, with 9 patients (69%) experiencing no nausea or vomiting; a further 3 had only mild symptoms and only one patient suffered WHO grade 3 toxicity. Three patients developed WHO grade 2 neutropenia and three had grade 3 neutropenia. Three patients experienced WHO grade 1 thrombocytopenia; another three had grade 2, 2 developed grade 3 and 1 had grade 4. Three patients required dose reduction because of this toxicity. One patient died during treatment due to progressive disease with intestinal obstruction.

Discussion

Metastatic carcinoid tumours do not usually respond well to chemotherapy. Doxorubicin and 5-FU are probably the two most active agents, but their response rates are generally low, ranging from 18% to 26% [2, 5]. In a previous study [6], single-agent cisplatin achieved an objective response in only 1 of 15 patients (7%). Response rates of 20%–40% have been reported for various combination regimens [3], and an Eastern Cooperative Oncology Group

randomised trial comparing combination streptozocin and 5-FU with single-agent doxorubicin found response rates of 22% and 21%, respectively [2]. Higher doses of streptozocin and 5-FU achieved a higher response rate of 33% in a previous ECOG trial [4], but this was associated with unacceptable toxicity.

The present study suggests that carboplatin, like other cytotoxic agents, has only limited activity in the management of metastatic carcinoid tumours, despite its high activity against small-cell lung cancer. However, several patients achieved useful symptomatic relief, sometimes accompanied by significant decreases in 24-h urinary 5-HIAA excretion. This result was achieved with low toxicity and suggests that the agent might play a role in symptom control in cases where other forms of therapy have proved to be ineffective. These observations might also serve as a basis for considering the use of carboplatin as part of combination therapy regimens. The minor tumour regression and good symptomatic relief seen in one of the two patients with metastatic paraganglioma suggests that carboplatin deserves further study in this rare condition.

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