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Short communication

Pilot study of escalating doses of carboplatin and cyclophosphamide in patients with advanced cancer

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Summary. In all, 18 patients with histologically proven advanced cancer received 400 mg/m^2 carboplatin (CBDCA) plus 800 mg/m^2 cyclophosphamide (level 1), and 14 others received 550 mg/m^2 CBDCA plus 1100 mg/m^2 cyclophosphamide (level 2). A maximum of six cycles was given if a response occurred. The dose-limiting toxicity was myelosuppression, with neutropenia being more marked than thrombocytopenia. At level 2, patients experiencing a febrile-neutropenic event showed a mean 24-h urinary creatinine clearance value of 1.1 ml/s (95% confidence limits 0.8–1.4 ml/s), whereas in those who remained afebrile it was 1.7 ml/s (95% confidence limits, 1.3–2.0 ml/s). This difference was significant (P <0.01). Other toxicities were only mild. Creatinine clearance is a predictor of febrile episodes after treatment with high doses of CBDCA and cyclophosphamide. We are now conducting a study using human granulocyte colony-stimulating factor to reduce the incidence of neutropenia with escalating doses of these drugs in an attempt to prevent febrile events.

Introduction

Carboplatin (CBDCA) has been demonstrated to show significant activity against several malignancies, including ovary, lung (small-cell and non-small-cell), head and neck, testicular and bladder cancers [5]. The combination of CBDCA and cyclophosphamide is highly active against some of these diseases and is currently regarded by some groups as the treatment of choice in carcinoma of the ovary [2]. The dose-limiting toxicity of this combination is myelosuppression, especially leukopenia [1].

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Prior to the initiation of a phase I study investigating the escalation of CBDCA and cyclophosphamide doses using recombinant human granulocyte colony-stimulating factor (rhG-CSF) to modify neutropenia, we conducted a pilot phase I study of escalating doses of CBDCA and cyclophosphamide in previously treated and untreated patients with advanced malignancy and related the findings with renal function.

Patients and methods

A total of 32 patients who had been referred to the Medical Oncology Unit, Royal Melbourne Hospital, Melbourne, Australia, were entered into the present study. These included 19 men and 13 women (median age, 60 years; range, 42–71 years) who had a variety of solid tumors. Nine patients had received prior treatment with non-platinum chemotherapy, and one subject had previously been given cisplatin. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

Subjects were given 2 l normal saline i.v. over 8 h prior to CBDCA administration and subsequently underwent i.v. infusions of 500 ml mannitol (10% solution) over 0.5 h and 4 l normal saline over 24 h. CBDCA was then given i.v. in 500 ml normal saline over 0.5 h. Cyclophosphamide was administered i.v. in 250 ml 5% dextrose over 0.5 h. (Intensive prehydration was performed in anticipation of a planned escalation study with rhG-CSF so as to minimize the potential for non-hematological toxicity due to CBDCA- and cyclophosphamide-induced hemorrhagic cystitis.)

Successive groups of patients were treated with 400 mg/m^2 CBDCA and 800 mg/m^2 cyclophosphamide (level 1, 18 subjects) or with 550 mg/m^2 CBDCA and 1100 mg/m^2 cyclophosphamide (level 2, 14 patients). Treatments were given every 21 days or after subjects had recovered from myelosuppression. Table 1 shows the number of patients and the average number of courses completed at both levels. Five subjects treated at both dose levels had received prior chemotherapy.

Pretreatment evaluation consisted of a complete history and physical examination, a full blood count (FBC), determinations of plasma urea and electrolytes and of 24-h urinary creatinine clearance and liver-function tests. Radiological examinations were carried out as indicated to document tumor extent. After the first course, an FBC was done at least every other day during myelosuppression and toxicities and vital signs were monitored. Weekly FBCs were done after subsequent courses. Plasma urea and electrolyte determinations and liver-function tests were done prior to each treatment.

Table 1. Number of patients and average number of courses of CBDCA and cyclophosphamide

CBDCA/ cyclophosphamide dose	Number of patients	Average number of courses (range)
Level 1 400/800 mg/m^2	18	3.2 (1–6)
Level 2 550/1100 mg/m^2	14	2.4 (1–6)

Table 2. Neutropenic toxicity after the first cycle of CBDCA/cyclophosphamide at the two dose levels tested

	CBDCA/cyclophosphamide dose	
	Level 1: 400/800 mg/m^2	Level 2: 550/1100 mg/m^2
Median neutrophil nadir (range)	0.4×10^9/l ($0.1-2.3\times10^9$/l)	0.2×10^9/l ($0.1-1.3\times10^9$/l)
Number of patients developing grade 4 neutropenia ($<0.5\times10^9$/l)	8	12
Median duration of grade 4 neutropenia in days (range)	4 (3–6)	7 (4–10)
Febrile episodes	2	7

Toxicity was assessed using WHO criteria [10]. Patients were observed for response, and therapy was continued to a maximum of six cycles if a response occurred. The chi-square test was used to examine the effects of renal function on hematological toxicities. Student's paired *t*-test was used to compare mean creatinine clearances in patients who experienced febrile episodes and those who did not. All subjects gave written, informed consent in accordance with institutional policy prior to their entrance into the study.

Results

Myelosuppression was the major toxicity observed. Median neutrophil count nadirs after the first course were 0.4×10^9/l (range, $0.02-2.3\times10^9$/l) for level 1 and 0.2×10^9/l (range, $0.06-1.3\times10^9$/l) for level 2. The number of patients experiencing grade 4 neutropenia was 8 at level 1 and 12 at level 2, for a median duration of 4 (range, 3–6) and 7 days (range, 4–10 days), respectively. Two febrile episodes were encountered at level 1 and seven, at level 2 (Table 2). Median platelet count nadirs were 75×10^9/l (range, $9-238\times10^9$/l) and 67×10^9/l (range, $15-112\times10^9$/l) at levels 1 and 2, respectively. Two patients at level 1 and one at level 2 experienced grade 4 thrombocytopenia. There was a single episode of minor bleeding in both groups.

Median 24-h urinary creatinine clearance was similar in the two groups. At level 1 it was 1.2 ml/s (range, 0.6–2.4 ml/s) and at level 2 it was 1.3 ml/s (range, 0.6–2.3 ml/s). There was a significant correlation between creatinine clearance and the occurrence of a febrile episode at level 2 but not at level 1. In patients who experienced a febrile episode the mean creatinine clearance was 1.1 ml/s (95% confidence limits, 0.8–1.4 ml/s), whereas in those who did not, it was 1.7 ml/s (95% confidence limits, 1.3–2.0 ml/s; $P<0.01$). No correlation was found between creatinine clearance and grade of neutropenia in either group.

All patients experienced at least mild nausea; however, when vomiting occurred, it was only transient and could be successfully treated with antiemetics. Other toxicities were only minor. No adverse renal or neurological effect was observed. There was no treatment-related death.

Discussion

CBDCA is a cisplatin analogue that has been shown to be a clinically active drug that produces qualitatively different or less severe toxicities than cisplatin. Its major side effect is myelosuppression, with thrombocytopenia being the dose-limiting toxicity; neutropenia occurs to a lesser extent. Little emesis, nephrotoxicity, neurotoxicity or ototoxicity is associated with its use [7]. Renal excretion accounts for 65% of the elimination of CBDCA, and the plasma clearance of the drug is directly correlated with glomerular filtration rate [8]; this linear relationship persists even at high doses [3]. The major factors determining toxicity are pretreatment renal function and a prior history of chemotherapy [11]. These observations have led to the formulation of dosing equations that have prospectively been found to lead to accurate predictions of drug exposure and, hence of the development of thrombocytopenia [4, 7]; however, these formulae are applicable only to single-agent therapy.

Cyclophosphamide, a commonly used alkylating agent, is mostly metabolized by the liver, with only 15% of the parent compound being excreted in the urine. Most of its activity is attributable to a complex array of metabolites that have proved to be difficult to isolate and measure [6]. However, myelosuppression has been shown to correlate with a prolonged serum half-life of cyclophosphamide in patients with renal impairment [9].

The dose-limiting toxicity of the combination of CBDCA and cyclophosphamide is myelosuppression, particularly leukopenia [1]. As the doses are escalated, leukopenia becomes more severe and prolonged, and this is clinically expressed as an increase in the frequency of febrile neutropenic episodes. In this small pilot study, we found 24-h creatinine clearance to be a predictor of febrile neutropenic events in patients receiving high doses of CBDCA and cyclophosphamide. That this was not observed at lower doses may in part be explained by the slightly smaller proportion of pretreated patients at level 1 as compared with level 2 (27% vs 35%). However, it is also likely to reflect the greater effect of impaired renal function on the toxicity of these drugs with increasing dose. We are currently performing a dose-escalation study of CBDCA and cyclophosphamide using rhG-CSF to ameliorate neutropenia.

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