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Clinical Trial Summary

A Phase II Study of Iproplatin in Advanced or Metastatic Stomach Cancer

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INTRODUCTION

CISPLATIN has been shown to have some activity in gastric cancer but its application is limited because of toxicity [1]. In recent years, the search for platinum compounds with reduced toxicity has been the main goal in the development of platinum analogs. Based on available phase I data [2, 3], our group decided to evaluate the antitumor activity of the non-nephro- and neurotoxic platinum derivative iproplatin [*cis*-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum(IV)].

MATERIALS AND METHODS

Twenty-eight patients with histologically confirmed, advanced or inoperable adenocarcinoma of gastric origin participated in the trial. Eligibility criteria also included measurable or evaluable disease with documented progression within the last 2 months, age ≤75 years, performance status of ≤2 (WHO), serum creatinine ≤ 120 μmol/l, WBC ≥ 4 × 10^9/l, platelet counts ≥ 100 × 10^9/l. Iproplatin was administered i.v. every 4 weeks at doses of 180 and 270 mg/m^2 in previously treated and untreated patients as recommended by Creaven *et al.* [3]. Untreated patients with a primary tumor still *in situ* or with ulcerated gastric lesions were given the reduced dose. The drug was supplied by Bristol-Myers International Corp., Brussels, in vials of 50 mg of iproplatin with mannitol. Each vial was reconstituted with 50 ml of isotonic saline, and the total dose was then infused over 1 h in 1000 ml of isotonic saline without any pre- or post-hydration. The dosage was modified according to the lowest value of WBCs and platelets measured weekly during the previous course. Specifically, the dose was increased by 25% in case of ≤grade 1 toxicity and was reduced by 20% or 40% in case of toxicity grade ≥3. Responses and toxicity grades were defined according to WHO criteria [4].

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RESULTS

Among 28 patients entered, two were subsequently defined as not eligible (histological diagnosis not available: one patient; bad physical conditions: one patient). Table 1 summarizes the characteristics of the remaining 26 eligible patients and the response to the treatment. Iproplatin was administered as first chemotherapy in 61% of the patients, in about half of the cases the stomach was the predominant localization, either as unresected primary or local recurrence.

The complete response of 52 weeks duration was surgically documented by peritoneoscopy and was reported in a previously untreated patient with neoplastic ascites, peritoneal carcinomatosis and subcutaneous abdominal recurrence. Iproplatin was discontinued after six cycles and was reintroduced without effect 7 months later at the time of recurrence.

Overall, three patients (11%) achieved an objective response, two (8%) had stable disease and 21 (81%) showed a tumor progression while on iproplatin.

Twenty-three patients, for whom weekly blood counts were available, were evaluable for hemato-

Table 1. Characteristics of eligible patients

Characteristics	No. of patients	No. of responders* CR	PR
Total	26	2 (16, 52)	1 (7)
Men/Women	18/8		
Median age in years (range)	63 (41–74)		
WHO performance status			
0–1	20		
2	6		
Previous surgery			
none	7		
palliative	7		1 (7)
radical	12	2 (16, 52)	
Previous chemotherapy			
none	16	1 (52)	
FAM†	10	1 (16)	1 (7)
Dominant localization			
primary tumour (not resected)	7		
local recurrence	6		
liver	8		1 (7)
soft tissue/skin	3	2 (16, 52)	
lung	1		
nodes	1		

*In parentheses, duration of response in weeks.
†F = 5-fluorouracil; A = Adriamycin®; M = mitomycin-C.

logical toxicity. Among nine pretreaed patients receiving a median iproplatin dose of 180 mg/m^2 (range 160–200), the median WBC and platelet nadir after the first cycle were 4.7 × 10^3/μl (range 2.4–11.4 × 10^3/μl) and 185 × 10^3/μl (range 132–300 × 10^3/μl). Among 14 non-pretreated patients receiving a median iproplatin dose of 240 mg/m^2 (range 180–270) the median WBC and platelet nadir after the first cycle were 5.3 × 10^3/μl (range 3.4–10.4 × 10^3/μl) and 127 × 10^3/μl (range 55–240). At the second cycle the dose had to be reduced in one pretreated patient but could be increased in 11 (three pretreated, eight untreated). Nausea and vomiting were almost universal (grade 2 and 3: 46 and 30%); diarrhea occurred in 35% (grade 2 and 3: 15 and 4%).

DISCUSSION

The results of this study indicate limited antitumor activity of iproplatin in gastric cancer (95% confidence intervals in the untreated group: 0–30%; in the pretreated group: 2–55%). This minimal response rate is comparable to that observed with carboplatin [5].

The lack of significant thrombocytopenia and the low incidence of the other dose-limiting toxicity, diarrhea, suggest that in the current study the initial dosage of iproplatin could have been substantially increased. In view of the low response rate achieved with the recommended dose of 270 mg/m^2 in previously untreated patients, it is unlikely, however, that higher doses could have resulted in better antitumor activity.

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