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Short communication

Phase II trial of continuous-infusion iproplatin (CHIP) and 5-fluorouracil (5-FU) in advanced colorectal carcinoma

Nicholas J. Petrelli[1], Patrick J. Creaven[2], Lemuel Herrera[1], and Arnold Mittelman[1]

[1] Roswell Park Memorial Institute,
[2] Department of Surgical Oncology and Clinical Pharmacology and Therapeutics*, Buffalo, NY, USA

Summary. Following the observation of antitumor activity for the combination of 5-fluorouracil (5-FU) and cisplatin in metastatic colorectal carcinoma, the combination of 5-FU and iproplatin was tested, also in colorectal carcinoma, in the hope of attaining equivalent activity without the nephrotoxicity observed with 5-FU/cisplatin. However, no responses were achieved with 5-FU/iproplatin.

Introduction

In a previous study we demonstrated activity for the combination of 5-fluorouracil (5-FU) with cisplatin [5] in metastatic colorectal carcinoma confirming the data reported by others [2]. In the earlier study, the dose-limiting toxicity of the combination was a decrease in creatinine clearance necessitating a reduction in the dose of cisplatin. Because iproplatin (*cis*-dichloro-*trans*-dihydroxy-isopropylamine CHIP) has no nephrotoxicity [1, 4] and has demonstrated antitumor activity [3], we combined 5-FU with iproplatin in an attempt to retain the activity while eliminating the nephrotoxicity of the combination of 5-FU and cisplatin.

Materials and Methods

Fourteen patients with measurable, histologically confirmed, advanced colorectal carcinoma were entered into this trial. Patient characteristics are outlined in Table 1. All patients had ECOG performance status 0 (normal activity), 1 (ambulatory but symptoms), or 2 (in bed less than 50% of time).

The starting dose in the first patients was iproplatin 30 mg/m^2 per day diluted in 1000 ml normal saline and 5-FU 600 mg/m^2 per day diluted in 1000 ml dextrose (5%) and water, given through separate intravenous lines over 24 h, for 5 days (1 course) every 4 weeks. Iproplatin doses were escalated by 10 mg/m^2 per course until toxicity precluded further escalation. An adequate drug trial comprised one course with toxicity.

Results

Four patients started iproplatin at a dose of 30 mg/m^2. In one of these patients the daily dose was escalated to 40 mg/m^2; 10 other patients started iproplatin at a dose of 40 mg/m^2 daily. Eight courses of iproplatin 30 mg/m^2 and 30 courses of iproplatin 40 mg/m^2 were completed.

All patients were evaluable for toxicity. Myelosuppression was the most common toxicity. Only two patients required dose reductions of 5-FU secondary to WBC nadirs of 2600/mm^3 and 2400/mm^3 respectively. One of these patients received a total of four courses, three of which required 5-FU reductions to 500 mg/m^2 (iproplatin 40 mg/m^2). The other patient completed six courses; in the second course the dose of 5-FU required was 500 mg/m^2 (iproplatin 40 mg/m^2) and the remaining four courses, 5-FU 400 mg/m^2 (iproplatin 40 mg/m^2 courses 3 and 4; 30 mg/m^2 courses 5 and 6). A total of six patients developed leukopenia, one patient at iproplatin 30 mg/m^2 and the remaining 5 at iproplatin 40 mg/m^2. The median nadir WBC was 2800/mm^3 (range 2400–3800/mm^3). The median number of courses administered before a nadir leukopenia occurred was two (range 1–6).

Thrombocytopenia occurred in four patients, all at iproplatin 40 mg/m^2. The median nadir platelet count was 89000/mm^3 (range 75000–98000/mm^3). The median number of courses administered before a nadir thrombocytopenia occurred was three (range 1–5).

Table 1. Patient characteristics

	Number of patients
Total	14
Sex	
Males	12
Females	2
Age in years	
Median 57	
Range 39–68	
Prior 5-fluorouracil treatment	14
Indicator lesions	
Liver	8
Lung	6
Toxicity	
Stomatitis (mild)	3
Thrombocytopenia ($\geq$75 000 $\leq$98 000/mm^3)	4
Leukopenia ($\geq$2400 $\leq$3800/mm^3)	6
Diarrhea (no i.v. hydration required)	3
Nausea and/or vomiting (controlled with antiemetics)	10

Offprint requests to: Nicholas J. Petrelli, Department of Surgical Oncology, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263, USA

Nausea and/or vomiting occurred in the majority of patients, but were controlled with antiemetics and did not preclude continued treatment. No significant decreases in creatinine clearance requiring a dose reduction of iproplatin occurred. No responses were seen in patients treated according to the regimen described.

We conclude that the maximum tolerated doses of iproplatin and 5-FU in combination given as a continuous 24 h infusion daily for 5 days are 40 mg/m^2 and 500 mg/m^2, respectively. In contrast to the combination of 5-FU and cisplatin, 5-FU and iproplatin brought about no responses in this group of previously treated patients. Myelosuppression was the dose-limiting toxicity for this regimen.

References

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