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Multicenter phase II study of brequinar sodium in patients with advanced gastrointestinal cancer

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Summary

Eighty-six patients with advanced colorectal, gastric or pancreatic carcinoma and no prior exposure to chemotherapy were treated with brequinar sodium. Brequinar was administered at a median weekly dose of 1200 mg/m^2 intravenously. The toxicity was moderate, with thirty patients (35%) experiencing grade 3 or 4 toxicity. Objective responses were observed in 1/32 evaluable colorectal and 2/29 evaluable gastric carcinoma patients. There were no objective responses in 17 evaluable pancreatic cancer patients. We conclude that, at this dose and schedule, brequinar does not have sufficient activity in these gastrointestinal malignancies to warrant further evaluation.

Introduction

Brequinar is a novel antimetabolite which interferes with dihydrooratate dehydrogenase, an enzyme crucial for pyrimidine biosynthesis [1]. Brequinar was selected for clinical development because of its broad antitumor activity in murine models (L1210 leukemia and B16 melanoma) and human tumor xenografts (breast MX-1), colon (CX-1), lung (LX-1), and gastric (BL/STX-1) [2].

A number of phase I studies utilizing different dose levels and schedules have been reported [3–8]. In these phase I studies, the dose-limiting toxicities included thrombocytopenia and mucositis/stomatitis. Minor responses were seen in advanced bladder, lung, lymphoma and thyroid carcinoma [3, 5, 8]. The weekly schedule was selected for phase II evaluation because of the superior dose intensity achieved in comparison with that previously obtained in the phase I schedules. In addition, the pharmacokinetic profile indicated a half-life of 15 hours, resulting in prolonged drug exposure when this schedule was used [3]. Preclinical studies also suggested that efficacy was achieved by prolonged exposure [9, 10].

On the basis of the phase I experience, the recommended phase II starting dose and schedule was 1800 mg/m^2 weekly [5, 6]. Early in the phase II evaluation of brequinar in several tumor categories, this starting dose resulted in unacceptable toxicity [11]. Therefore, the starting dose was reduced to 1200 mg/m^2 weekly. This multicenter study was designed to evaluate the activity of brequinar in patients with advanced colorectal, gastric or pancreatic carcinoma who had received no prior chemotherapy.

Patients and methods

Criteria for inclusion in the study were performance status of ≤ 2 (WHO scale), life expectancy

Table 1. Patient and treatment characteristics

Characteristics	Colorectal	Gastric	Pancreas
Total patients	35	32	19
(inevaluable/not eligible)	(3/2)	(3/1)	(2/0)
Male:Female	25/10	28/4	14/5
Median age (range)	62 (40–75)	66 (37–79)	62 (25–72)
Performance status*			
0	14	10	8
1	16	19	8
2	5	3	3
Prior therapy			
Surgery	35	26	11
Radiation therapy	4	4	0
Biological therapy	3	0	0
Chemotherapy	0	0	0
Sites of metastases (%)			
Liver	25 (71)	21 (66)	13 (68)
Lung	12 (34)	5 (16)	1 (5)
Lymph nodes	6 (17)	8 (25)	3 (16)
Skin/subcutaneous tissue	0 (0)	4 (12)	0 (0)
Other	9 (26)	9 (28)	4 (21)

*World Health Organization criteria [12].

> 8 weeks, serum bilirubin < 1.5 mg/dl, serum creatinine < 2.0 mg/dl, absolute granulocyte count > 1,500 cells/mm^3, platelet count > 100,000/mm^3, and presence of bidimensionally measurable disease. Informed consent was given by all patients in accordance with regulatory agency requirements.

Brequinar was administered intravenously once weekly at a starting dose of 1800 mg/m^2 (8 patients) or 1200 mg/m^2 (78 patients) in 500 ml of normal saline over 1–2 hours. The subsequent dose of brequinar was escalated or decreased according to predetermined criteria and depending on the toxicities experienced in the preceding course. When necessary, dosing was delayed until the patient recovered from toxicities. Toxicity was coded by NCI common toxicity criteria (2/18/88 version). Patients were interviewed and examined prior to each dose of chemotherapy. Laboratory studies including complete blood cell, differential, and platelet counts were repeated once a week. Total protein, albumin, calcium, inorganic phosphorous, glucose, blood urea nitrogen, creatinine, uric acid, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and electrolytes were assessed every four weeks.

Response was evaluated every four weeks by appropriate radiologic studies and clinical measurement of bidimensional lesions. Criteria for defining response were standard; except, palpable reduction in liver size was not utilized to designate a partial response. Patients were considered evaluable for response if they received at least one dose of brequinar and underwent a subsequent assessment of their measurable disease. Patients who died of disease without such an assessment were considered evaluable and classified as progressive disease.

Results

From November 1988 to December 1990, 86 patients with histologically documented, advanced, measurable colorectal, gastric or pancreatic carcinoma were entered in the study. Patient and treatment characteristics are listed in Table 1. The patients had excellent performance status and limited exposure to prior therapy. The predominant sites of measurable disease were liver, lung and lymph nodes.

Dosing and treatment results are presented in Table 2. The 86 patients received 441 doses of bre-

Table 2. Dosing and treatment results

	Colorectal	Gastric	Pancreas
Doses administered			
Total	219	140	82
Median	6	4	4
Range	1–15	1–11	1–8
Median weekly dose-mg/m^2	1200	1200	1200
Range	(588–3110)	614–2300)	(960–1800)
Number of patients			
Dose escalation	13	8	7
Dose reduction	11	11	3
Receiving one dose only	4	5	4
Treatment results			
Partial response	1	2	0
Stable disease	8	7	4
Progressive disease	23	20	13

Table 3. Toxicity (all patients)

Toxicity	No. of patients by maximum grade			
	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia	6	2	1	0
Fatigue	10	2	0	0
Nausea/vomiting	26	15	7	3
Mucositis/stomatitis	12	7	5	3
Rash	13	8	5	1
Diarrhea	18	10	2	1
Thrombocytopenia	8	15	5	7
Anemia	5	18	11	1
Leukopenia	9	7	2	0
Granulocytopenia	5	9	2	1

quinar (median 4, range 1–15). In 28 patients dose escalation was possible and in 25 patients dose reduction was required. Thirteen patients received only one dose. The median weekly dose was 1200 mg/m^2. Seventy-eight of the 86 patients were evaluable for response. Three patients were deemed ineligible due to the absence of a measurable lesion, and five additional patients were inevaluable due to early non-disease-related death and inability to obtain follow-up tumor measurements. Partial responses were observed in 2 gastric and 1 colorectal cancer patients. These responses were of 66, 100, and greater than 200 days duration respectively. There were no objective responses to patients with pancreatic cancer.

All 86 patients are evaluable for toxicity. In general, the toxicity encountered in this phase II trial was moderate. The major non-hematologic and hematologic toxicities encountered are listed in Table 3. There were two treatment related deaths in patients with metastatic gastric cancer. One patient with extensive peritoneal carcinomatosis experienced grade 4 thrombocytopenia and gastrointestinal bleeding after his first dose of brequinar (1800 mg/m^2). The second patient, with extensive hepatic metastasis and a history of diabetes, experienced grade 4 thrombocytopenia and progressive deterioration of renal function after receiving his eighth dose of brequinar (total dose 20 grams; starting dose 1200 mg/m^2). The deterioration in renal function in this case was in part attributable to contrast employed in the follow-up radiographic evaluation of measurable hepatic metastases.

Seventeen episodes of grade 4 toxicity occurred

in 12 (14%) patients (4 colorectal, 7 gastric, 1 pancreatic). In 3 patients (2 colorectal, 1 gastric) these grade 4 toxicities were associated with the 1800 mg/m^2 starting dose. The remaining instances of grade 4 toxicity occurred in patients whose starting dose was 1200 mg/m^2 and generally occurred during the early treatment doses. The grade 3 toxicities summarized in Table 3 occurred in 18 (21%) patients (9 colorectal, 6 gastric, 3 pancreatic). In 3 patients (2 colorectal, 1 gastric) the starting dose was 1800 mg/m^2. The remaining instances of grade 3 toxicity occurred in patients whose starting dose was 1200 mg/m^2.

Grade 3–4 toxicity was observed in 6 of the first 8 patients (75%) entered at the initial starting dose of 1800 g/m^2. However, subsequent reduction in the starting dose to 1200 mg/m^2 resulted in a more acceptable level of grade 3–4 toxicity (24/78 patients, 30%). Dose escalation was possible in 32% (28/86) of patients; however, despite the reduction in starting dose, a further dose reduction was required at some point in the course of treatment in 29% (25/86) of patients. The reduction in starting dose followed by additional escalations and reductions based on individual patient tolerance account for the wide range (588–3110 mg/m^2) of doses administered to these patients with gastrointestinal malignancies. The observed variation in tolerance may, in part, reflect the magnitude of the hepatic involvement of individual patients in this study.

Discussion

The absence of objective responses in 17 evaluable patients with pancreatic cancer excludes a response rate of 20% (one-sided 95% confidence limit, 16%). In addition, response rates of 3% (1/32) in colorectal cancer (one-sided 95% confidence limit, 15%) and 7% (2/29) in gastric cancer (one-sided 95% confidence limit, 29%) are disappointing. On the basis of these results, we conclude that at this dose and on this schedule, brequinar sodium does not have sufficient activity to warrant further evaluation in patients with advanced gastrointestinal carcinoma.

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