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Research paper

Phase II study of paclitaxel in pretreated advanced gastric cancer

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Patients with advanced gastric cancer unresponsive or progressing after PELF chemotherapy (5-fluorouracil, leucovorin, cisplatin and epidoxorubicin) received paclitaxel at the dose of 225 mg/m^2 every 3 weeks, over 3 h infusion. Thirty-six patients entered the study, and all of them were evaluable for response and toxicity. Toxicity was mild: apart from alopecia, grade 3 toxicities were leukopenia and thrombocytopenia in six patients, and grade 2 neurotoxicity in seven patients. Eight patients (22.2%, 95% CI: 9–35%) achieved an objective response, with a median duration of 5 months. Median survival time for all patients was 8 months. In 16 of 36 patients (44%), treatment determined a significant relief of symptoms. Out-patient paclitaxel given over 3 h may be effective as salvage treatment in patients with advanced gastric cancer refractory to first line chemotherapy. [© 1998 Lippincott-Raven Publishers.]

Key words: Advanced gastric cancers, chemotherapy, paclitaxel.

Introduction

Metastatic gastric carcinoma remains an incurable disease with a median survival of only 4–8 months.[1] A number of chemotherapeutic agents are active in advanced carcinoma of the stomach. However, response rates yielded with these drugs and their combinations are low, with a duration of responses ranging between 6 and 9 months only. Therefore, finding an effective systemic chemotherapy is a high priority.[2] Paclitaxel, which acts as a mitotic spindle poison and induces a mitotic block,[3] has been shown to have antitumor activity in several tumors.[4] *In vitro*, drug concentrations similar to those achievable in clinical use have been shown to inhibit gastric carcinoma cell lines.[5] Furthermore, paclitaxel appears to have a definite level of activity against gastric carcinoma in phase I–II studies.[6,7] Recently, we completed a phase I study of escalating doses of paclitaxel in combination with a weekly fixed dose of 5-fluorouracil in previously treated gastric cancer patients. The maximum tolerated dose of paclitaxel was 225 mg/m^2 infused over 3 h.[8]

No active second-line chemotherapy is yet available for gastric cancer patients who have not responded or who have relapsed after initial response to first-line chemotherapy. Furthermore, these patients are often symptomatic and palliative care is not sufficient to control symptoms. This situation led us to verify in a phase II clinical trial the activity of paclitaxel in patients with advanced measurable gastric carcinoma which was refractory to a combination of cisplatin, epi-doxorubicin, leucovorin and 5-fluorouracil.

Patients and methods

Patients with histologically proven metastatic gastric carcinoma were included in this study. Admission criteria included: patients not responding (stable or progressive disease) to a combination chemotherapy including 5-fluorouracil, leucovorin, cisplatin and epidoxorubicin; age <70 years; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; presence of measurable disease; absence of concomitant disease and life expectancy >3 months. Furthermore, patients had to present adequate organ function (serum creatinine <1.5 mg/dl; BUN <50 mg/dl; bilirubin <1.5 mg/dl; SGOT, SGPT, alkaline phosphatase $<$three times the upper limit of normal; WBC count $>4000/mm^3$; platelet count $>100\,000/mm^3$). Prior chemotherapy had been stopped at least 2 months before.

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Prior to therapy, complete history, physical examination, tumor measurement, height, weight and performance status were recorded. Baseline values of complete blood cell count, platelet count, creatinine, total protein, albumin, SGOT, SGPT, alkaline phosphatase, bilirubin and electrolytes were obtained. History, physical examination, complete blood count, liver and kidney function tests were required before each paclitaxel administration. Furthermore, hemograms were repeated every week to record hematological toxicity.

Paclitaxel was administered as a 3 h infusion at the dose of 225 mg/m^2 repeated every 3 weeks. Dexamethasone 20 mg i.v., diphenydramine 25 mg i.v. and ranitidine 50 mg i.v. were given 30 min before paclitaxel.

Toxicity was recorded every week according to National Cancer Institute Common Toxicity Criteria (CTC).[9] Response was assessed according to standard WHO criteria.[10] All patients who received at least two cycles were evaluable for response.

Baseline assessment of symptoms (pain and dysphagia) was performed and their changes in intensity were recorded at each attendance. Patients were asked to grade symptoms (absent, low, moderate or high) and to report consumption of palliative medications (i.e. analgesics, corticosteroids, etc.).

A two-stage design was followed for this study so that the trial could be stopped early if the drug was inactive in this group of patients.

The primary objective was to determine the response rate and toxicity of paclitaxel; secondary objectives were to measure the duration of response and survival. According to the optimal two-stage phase II design, the treatment program was designed to reject a response rate less than 10% (p0) and to provide a statistical power of 90% in assessing the activity of the regimen (in terms of response rate as 30% (p1) (p1−p0=20%) for an α error less than 0.05.[11]

The 95% exact confidential interval (CI) for response was calculated. Survival time was calculated from the onset of chemotherapy. Informed consent was obtained from all participants after the nature of the study had been fully explained and the protocol was approved by the institutional review board.

Results

Thirty-six patients were entered into the trial between March 1995 and June 1996. All patients were not responsive (stable or progressive disease) to the PELF regimen. The patients' characteristics are listed in Table 1. A total of 128 cycles of chemotherapy were administered, with a median of 3 per patient (range 2-6).

Toxicity

Grade 3 leukopenia and thrombocytopenia was present in six patients. Seven patients experienced neurotoxicity grade 2; arthralgias and myalgias were seen in 26 patients but in only six patients were these considered severe and analgesics required (Table 2).

Table 1. Patient's characteristics

Age (years)	
median	61
range	40–68
Sex	
M/F	24/12
Performance status (ECOG)	
0	7
I	20
II	9
Prior surgery	
none	7
curative	21
palliative	8
Sites of primary tumor	
gastroesophageal junction	7
proximal stomach	4
body	18
distal stomach	7
Response to prior chemotherapy	
stable disease	19
progressive disease	17
Sites of metastases	
liver	13
lung	5
abdomen/peritoneum	8
local relapse	5
lymph nodes	10

Table 2. Maximum toxicity observed for each patient

Toxic effect	NCI CTC			
	1	2	3	4
Leukopenia	4	4	4	–
Thrombocytopenia	3	3	2	–
Neurotoxicity	2	7	–	–
Stomatitis	3	–	–	–

Response

All patients were evaluable for response, having received at least two cycles of chemotherapy. Eight patients achieved a partial response for an overall response rate of 22.2% (95% CI, 9-35%). Responses were seen in hepatic, lung and peritoneal metastases of patients with stable disease after first-line chemotherapy. Four patients had a minor response and 11 patients showed a stable disease while 13 progressed on therapy. Median duration of responses was 5 months. The median time to progression of all patients was 5 months; overall survival was 8 months.

In eight patients achieving a partial response, in four with a minor response and in four with stable disease, treatment determined a significant relief of symptoms. Pain reduced from high to low in six patients and in eight patients pain disappeared. Analgesic consumption was discontinued in eight patients and reduced in six patients. Dysphagia improved in five of the 10 patients with this symptom, while cough was seen in two out of three patients. Five patients discontinued corticosteroids.

Discussion

At present four drugs, 5-fluorouracil, doxorubicin, cisplatin and mitomycin C, have been identified as having reproducible modest to moderate single-agent activity in patients with advanced gastric cancer.[1] Clinical trials combining these cytotoxic agents have reported response rates of 30-40% but, unfortunately, complete responses have been uncommon, the duration of response short and the toxicity significant.[2]

New cytotoxic agents, such as irinotecan, a topoisomerase inhibitor, or taxanes, paclitaxel and taxotere, seem to be interesting innovative anticancer agents in gastric carcinoma.[6,7,12] Recently, Chang *et al.* found paclitaxel very effective in growth inhibition of gastric carcinoma cell lines, suggesting this drug has potential in the treatment of gastric cancer.[5] Interesting data in gastric cancer were reported by Sulkes *et al.* also with taxotere. Eight of 33 evaluable patients (24%) achieved a partial remission with acceptable toxicity.[13]

The activity of taxanes in gastric cancer could depend on the property of killing tumor cells in the absence of wild-type p53 function, so that, unlike other drugs needing wild-type p53, paclitaxel can be active also in tumors that frequently have p53 gene mutations, such as gastric cancer.[14,15]

At least two phase II studies have shown that paclitaxel had a low but definite activity against gastric carcinoma.[6,7] In a phase I study carried out at our institutions, the maximum tolerated dose of paclitaxel associated with a weekly fixed dose of 5-fluorouracil was 225 mg/m^2. Toxicity was acceptable and activity was confirmed.[8]

In the present study, paclitaxel was given at the maximum tolerated dose found in the phase I study, but it was not associated to 5-fluorouracil. In fact, because patients failed to respond to the previous chemotherapeutic regimen which included 5-fluorouracil, this drug was considered to be unlikely to be active in the same patients as second-line chemotherapy.

We obtained a response rate of 22.2% and a symptom palliation in about 40% of patients. This symptomatic effect was recorded in all patients achieving a partial or minor response and in four patients, with a stable disease, achieving a reduction in tumor mass of about 10-15%. These data seem to suggest that in patients with advanced gastric cancer a less than 50% decrease in measurable tumor bulk may be associated with a clinical benefit. The symptomatic effect obtained in these patients may be of particular interest since most advanced gastric cancer patients complain of pain, vomiting and other symptoms not sufficiently controlled by palliative care alone.

In conclusion, paclitaxel can be safely administered to patients with advanced gastric cancer representing a novel active and low toxic drug even in pretreated patients. The relatively low toxicity of paclitaxel with its definite activity in terms of response rate and symptom control could also be of interest in untreated gastric cancer patients, who, because of age and poor performance status, often cannot receive aggressive chemotherapy.

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