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Short Communication

A Phase I Study of Paclitaxel and 5-Fluorouracil in Advanced Gastric Cancer

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This is a phase I study to determine the maximum tolerated dose (MTD) and toxicity of a combination of paclitaxel and 5-Fluorouracil (5-FU) in advanced gastric cancer patients. The patients, refractory to the PELF regimen (5-FU, leucovorin, cisplatin, epidoxorubicin), received weekly 5-FU at the fixed dose of 500 mg/m^2, and escalating doses of paclitaxel every 3 weeks with a starting dose of 150 mg/m^2 given as in 3-h infusion. The dose was escalated by 25 mg/m^2 every 3 patients. Fifteen patients entered the study. The upper paclitaxel dose (225 mg/m^2) was given to 6 patients. Up to this dose, no severe toxicity (grade 3–4) was recorded. Apart from alopecia, grade 1–2 leukopenia occurred in 5 patients and grade 1–2 neurotoxicity in 2 patients. All patients were evaluable for response (at least 2 cycles): 2 patients achieved an objective response (200 and 225 mg/m^2). In 6 patients, treatment resulted in notable relief from symptoms. Out-patient paclitaxel given over 3 h and 5-FU may be combined safely for the treatment of patients with advanced gastric cancer. The recommended doses for phase II study are paclitaxel 225 mg/m^2 and 5-FU 500 mg/m^2. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

METASTATIC GASTRIC carcinoma remains an incurable disease with a median survival of only 4–8 months. Although several new chemotherapeutic regimens have produced initially high response rates, these successes have not been subsequently confirmed, so the identification of an active treatment is a high priority in advanced gastric cancer [1].

Paclitaxel is a new important antitumour compound acting as a mitotic spindle poison and inducing a mitotic block [2]. Antitumour activity has been documented in several tumours [3]. *In vitro* concentrations, similar to that attainable in clinical use, have been demonstrated as active in inhibition of gastric carcinoma cell lines [4].

5-fluorouracil (5-FU) remains a common element in combination chemotherapy regimens for gastric cancer. Because the combination of paclitaxel and 5-FU has demonstrated additive cytotoxicity in tumour cell lines [5, 6] and different mechanisms of action and resistance as well as non-overlapping toxicities [1, 2, 7], a phase I study was initiated to determine the maximum tolerated dose (MTD) of paclitaxel in combination with 5-FU.

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PATIENTS AND METHODS

Patients with histologically proven metastatic gastric carcinoma were included in this study. Admission criteria included: patients refractory (stable or progressive disease) to the PELF regimen (5-FU, leucovorin, cisplatin, 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; GOT, GPT, alkaline phosphatase < three times the upper limit of normal; WBC (white blood cell) count > 4000/mm^3; platelet count > 100 000/mm^3). Prior chemotherapy was allowed if treatment had been stopped at least 2 months previously.

All patients gave their informed consent to participate in the study.

Prior to therapy, complete clinical history, physical examination, tumour measurement, height, weight and performance status were recorded. Baseline values of complete blood cell count, platelet count, creatinine, total protein, albumin, GOT, GPT, alkaline phosphatase, bilirubin and electrolytes were obtained. Clinical history, physical examination, complete blood count, liver and kidney function tests were required before each paclitaxel administration. Furthermore, haemograms were repeated every week to record haematological toxicity.

Drug administration

5-FU was given weekly at the fixed dose of 500 mg/m^2 as a 15-min infusion in 100 mL of normal saline solution. The starting dose of paclitaxel was 150 mg/m^2 given over 3 h. The dose in cohorts of 3 patients was escalated by 25 mg/m^2. Dosages were not escalated over successive treatment courses for individual patients.

Three evaluable patients were entered at each dose level. Subsequent dose levels were not opened until safety and tolerance were assessed at the previous dose level for all 3 patients for two complete cycles. If dose-limiting toxicity (DLT) of any type was seen in one of the 3 patients within the first two cycles of treatment, a further 3 patients were enrolled. If 2 or more of the 6 patients experienced DLT, this level was considered the maximum tolerated dose (MTD), and the previous level considered the recommended phase II dose. Once determined, the phase II dose level was expanded to obtain more detailed toxicity and feasibility data [8].

DLT was defined as (1) an absolute granulocyte count $< 0.5 \times 10^9$/L for 7 or more days or the development of infection or fever requiring parenteral antibiotics, (2) a platelet count $< 50 \times 10^9$/L (grade 3) for 7 or more days, the requirement of two or more platelet transfusions within one cycle, or grade 2 or greater haemorrhage, (3) grade 3 or greater non-haematological toxicity with the exception of alopecia or (4) dose reductions and/or treatment delays for longer than 1 week for reasons of toxicity. Toxicity was recorded every week according to National Cancer Institute Common Toxicity Criteria [9]. Response was assessed according to standard WHO criteria [10]. All patients who received at least two cycles were evaluable for response.

RESULTS

Fifteen patients were entered into the trial between October 1995 and March 1996. All patients were refractory to a combination of 5-FU, leucovorin, cisplatin and epidoxorubicin. The patients' characteristics are listed in Table 1. A total of 46 cycles of chemotherapy were administered, with a median of 2 per patient (range 2–6).

Toxicity and maximum tolerated dose

All patients were fully evaluable for toxicity. Table 2 summarises the incidence of certain toxic effects occurring at the various dosage levels. Dose-limiting haematological toxicity during cycles 1 and 2 did not occur in any patient even at the paclitaxel dose level of 225 mg/m^2. This dose level was, however, expanded to further 3 patients, but no toxicity grade 3–4 was recorded.

Table 1. Patients' characteristics

Age (years)	
Median	60
Range	38–73
Sex	
M/F	10/5
Performance status (ECOG)	
0	4
I	10
II	1
Prior surgery	
None	2
Curative	10
Palliative	3
Sites of primary tumour	
Gastro-oesophageal junction	3
Proximal stomach	1
Body	10
Distal stomach	1
Prior chemotherapy	15
Sites of metastases	
Liver	7
Lung	1
Abdomen/peritoneum	4
Local relapse	3
Lymph nodes	4

Non-haematological toxicity was modest. 2 patients (175 mg/m^2 and 225 mg/m^2) experienced neurotoxicity grade 2, and 1 patient (225 mg/m^2) complained of stomatitis grade 2. Arthralgias and myalgias were seen in all the patients receiving paclitaxel at the dose of 225 mg/m^2. In 4 patients they were moderate but in 2 were considered severe and analgesics were required.

Response

All patients were evaluable for response, having received at least two cycles of chemotherapy. One patient achieved a complete response (200 mg/m^2) and one a partial response (225 mg/m^2) for an overall response rate of 13% (95% CI 10–16%). Both responses were seen in hepatic metastases of patients with stable disease after first-line chemotherapy. 6 patients showed a stable disease, while 7 progressed on therapy. In 6 patients, treatment resulted in a notable relief of symptoms (pain, dysphagia, cough).

DISCUSSION

Currently four drugs, 5-FU, 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 [1].

New cytotoxic agents, such as irinotecan, a topoisomerase inhibitor, or paclitaxel and taxotere, representative of taxoids, seem to be interesting innovative anticancer agents in gastric carcinoma [11]. Recently, Chang and associates found paclitaxel so effective in growth inhibition of gastric carcinoma cell lines, and suggested that this drug had great potential for the treatment of gastric cancer [4]. Furthermore, interesting data in gastric cancer were reported by Sulkes and associates with taxotere. Eight of 33

Table 2. Toxic effects encountered according to paclitaxel dose levels

Toxic effect	NCICTC grade	Number of patients with toxicity			
		150 mg/m^2	175 mg/m^2	200 mg/m^2	225 mg/m^2
Leucopenia	1–2	–	1	2	2
	3–4	–	–	–	–
Thrombocytopenia	1–2	–	–	–	1
	3–4	–	–	–	–
Anaemia	1–2	–	–	–	1
	3–4	–	–	–	–
Neurotoxicity	1–2	–	1	–	1
	3–4	–	–	–	–
Diarrhoea	1–2	–	–	–	–
	3–4	–	–	–	–
Stomatitis	1–2	–	–	–	1
	3–4	–	–	–	–
Arthralgia/myalgia	moderate	–	–	1	4
	severe	–	–	–	2

NCICTC, National Cancer Institute Common Toxicity Criteria

evaluable patients (24%) achieved a partial remission with acceptable toxicity [12].

Because 5-FU and paclitaxel have additive cytotoxicity in different tumour cell lines [5–7] and nonoverlapping toxicities, a phase I study was initiated to evaluate the feasibility of such a combination. Our patients were heavily selected, particularly performance status (0–2), in order to reduce the risks of severe toxicity.

Our results show that paclitaxel, every 3 weeks, may be combined safely with a common weekly schedule of 5-FU in patients with advanced gastric cancer. Apart from alopecia, toxicity was mild: the worst side-effect was grade 2 leukopenia in 5 patients (1, 175 mg/m^2; 2, 220 mg/m^2, 2, 225 mg/m^2) and grade 1–2 neurotoxicity in 2 patients (Table 2). This low incidence of myelosuppression might be explained by the use of 3-h infusion to allow for a more convenient out-patient schedule, instead of a 24-h infusion. In a randomised trial on ovarian cancer, a 24-h infusion was associated with significantly more myelosuppression than a 3-h infusion, but not with a higher response rate [13]. Similar data have been recently reported by Sheperd and associates in non-small cell lung cancer [14].

Arthralgias and myalgias for 2 or 3 days after paclitaxel administration were present in all 6 patients receiving a dose of 225 mg/m^2. In 4 patients, these side-effects were moderate, but in 2 they were severe and analgesics were required. Since previous studies have shown that the prolonged administration of higher paclitaxel doses is poorly tolerated by patients because of myalgia and neurotoxicity [15, 16], we elected to close the study, although DLT was not encountered at a paclitaxel dose of 225 mg/m^2.

This study was designed as a phase I dose-finding trial, but it has also been possible to assess the activity of this combination. Two patients achieved an objective response: a complete response at a paclitaxel dose of 200 mg/m^2 and a partial response at a dose of 225 mg/m^2. These results are not particularly exciting. However, all our patients had been pretreated and were not responsive to a chemotherapy combination including cisplatin, epi-doxorubicin, 5-FU and leucovorin [17].

The relatively low toxicity with definite activity of taxanes could be of interest for the treatment of gastric cancer patients, who, because of age and poor performance status, often cannot receive aggressive chemotherapy.

In conclusion, paclitaxel and 5-FU can be safely combined and could represent a novel, active and low toxicity combination in advanced gastric cancer. Further phase II studies could define the activity and safety of this combination.

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