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Short report

Escalating dose of tegafur combined with oral etoposide in metastatic gastric carcinoma

Stefano Cascinu and Giuseppina Catalano
Servizio di Oncologia, Ospedali Riuniti, P. le Cinelli 4, 61100 Pesaro, Italy. Fax: (+39) 721-362592.

Fifteen patients with advanced gastric cancer received orally etoposide 100 mg daily for 14 days and escalating doses of tegafur. The starting dose was 400 mg daily. The maximum tolerated dose of tegafur was identified at 850 mg daily. Unacceptable toxicity was seen at 1000 mg, and consisted of diarrhea, stomatitis and leukopenia. Two partial responses were seen at 800 mg daily. In conclusion, our data show that etoposide and tegafur can be safely administered in combination by the oral route.

Key words: Gastric carcinoma, oral etoposide, tegafur.

Introduction

Metastatic gastric carcinoma remains an incurable disease with a median patient survival of only 4–8 months. Although several new chemotherapeutic regimens have produced initially high response rates these successes were not subsequently confirmed, thus the identification of an active systemic chemotherapy is a very high priority in advanced gastric cancer.[1]

Etoposide has been reported to be effective in advanced gastric cancer and it may be safely combined with 5-fluorouracil (5-FU).[2,3] Recently, the efficacy and safety of chronic oral administration of etoposide for 14–21 days have been demonstrated in a variety of tumors.[4–6] Preliminary data seem to show an interesting activity also in advanced gastric cancer.[7]

Because 5-FU is active in gastric cancer and experimental data have indicated synergy between 5-FU and etoposide, as well as the lack of cross-resistance, it was our intention to evaluate the feasibility of an oral combination of 5-FU and etoposide.[8,9]

Tegafur, a 5-FU prodrug, was used because it seems to present better pharmacological properties than 5-FU in oral adminstration.[10]

Correspondence to S Cascinu

Patients and methods

Patients with histologically proven metastatic gastric carcinoma were included in this study. Admission criteria included an age <75 years; an Eastern Cooperative Oncology Group (ECOG) performance status 0–2; the presence of measurable disease; the absence of concomitant disease and a life expectancy of >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, phosphatase alkalyne $<$ three times the upper limit or normal; WBC count $>4000/mm^3$; platelet count $>100\,000/mm^3$).

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

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, GOT, GPT, alkaline phosphatase, bilirubin and electrolytes were obtained. History, physical examination, complete blood count, and liver and kidney function tests were required before each course of therapy. Furthermore, hemograms were repeated every week to record hematological toxicity.

Response and toxicity were assessed according to standard WHO criteria.[11] All patients who received at least one cycle were evaluable for toxicity, while patients were also considered evaluable for response after receiving two cycles of chemotherapy.

Drug administration

Tegafur was administered orally for 14 days. It was studied in a phase I fashion using a modified Fibonacci schedule.[12] The starting dose was 400 mg daily. Dose in cohorts of three patients was escalated by 200 mg daily. Dosages were not escalated

over successive treatment courses for individual patients.

The maximum tolerated dose (MTD) was defined to be one level below the dose producing unacceptable toxicity. The occurrence of grade 3–4 WHO toxicity of any type in two or more patients at a given dose was considered unacceptable. A minimum of six patients were treated at the dose determined to be the MTD.

Etoposide was given at a fixed dose of 100 mg daily for 14 days. Cycles were repeated every 3 weeks.

Results

Fifteen patients were entered into the trial. The patients' characteristics are listed in Table 1. All patients but one received two cycles of therapy. Two patients with objective response received a further two cycles of chemotherapy.

Response

Two partial responses (13%) were seen at 800 mg daily (Table 2). The response duration was 3 and 4 months. The median survival time for all patients was 7 months.

Table 1. Patients' characteristics

Age (years)	
median	68
range	48–72
Sex	
M/F	10/5
Performance status (ECOG)	
0	3
I	7
II	5
Prior surgery	
none	4
curative	9
palliative	2
Sites of primary tumor	
gastroesophageal junction	2
proximal stomach	4
body	7
distal stomach	2
Sites of metastases	
liver	5
lung	2
abdomen/peritoneum	6
lymph nodes	5
bone	1
Prior chemotherapy	15

Table 2. Dose level, patient entry and response to tegafur and etoposide

Tegafur (mg)	Etoposide (mg)	Eligible patients	Objective response
400	100	3	—
600	100	3	—
800	100	6	2
1000	100	3	—

Toxicity and MTD

Table 3 summarizes the incidence of certain toxic effects occurring at the various dosage levels. The MTD of tegafur was defined as 800 mg daily. Unacceptable toxicity began at 1000 mg and consisted of the following grade 3–4 toxicity: diarrhea in one patient; stomatitis in two patients; leukopenia in one patient.

Discussion

Etoposide has been shown to be active in advanced gastric cancer.[2,3] Although the best dose and schedule for etoposide administration remain unknown, being a cell-cycle specific agent, its degree of cytotoxicity most likely relies on duration of cell exposure. Thus etoposide may be particularly effective in low divided daily oral doses (50–100 mg daily) given for prolonged periods (14–21 days).[13] Clinical findings in several tumors seem to confirm the usefulness of chronically adminstered orally etoposide.[4–6].

Recently, preliminary results have also suggested an interesting activity in advanced gastric cancer.[7]

Because etoposide and 5-FU have resulted synergy in gastric cancer cell lines, as well as non-cross-resistance,[8] it was our intention to evaluate if it was possible to combine 5-FU, given orally, with oral etoposide at the dose of 100 mg daily for 14 days every 3 weeks. We decided to give a fixed dose of etoposide in a single daily administration since interpatient variation in surface area is much lower than variation in pharmacokinetics after oral etoposide administration, and no arguments favor fractioning a daily 100 mg etoposide dose.[13–15]

Tegafur is a 1-(tetrahydro-2-furanyl) derivative of 5-FU. It is gradually metabolized in the liver to a number of active components but mainly to 5-FU. In this way it acts as a depot cytostatic.[6,12]

Table 3. Toxic effects encountered according to tegafur dose levels

Toxic effect	WHO grade	No. of patients with toxicity			
		400	600	800	1000
Leukopenia	1–2	1	1	1	—
	3–4	—	—	—	1
Thrombocytopenia	1–2	—	—	1	1
	3–4	—	—	—	—
Anemia	1–2	—	1	1	1
	3–4	—	—	—	—
Diarrhea	1–2	—	—	1	—
	3–4	—	—	—	1
Stomatitis	1–2	—	1	1	—
	3–4	—	—	—	2

The bioavailability after oral administration seems to be total and higher than 5-FU.[10] Toxicity is not greater and this was especially true for the cumulative toxicity which is five to seven times greater after 5-FU administration than after tegafur treatment.[16] Furthermore, orally administered tegafur seems to exert a longer and more potent inhibitory effect on thymidilate synthetase than equimolar 5-FU, determining a possible advantage for the prodrug in oral route.[17]

The MTD of tegafur when given as a single agent has been found to be about 1200–1600 mg daily.[18,19] In the present study we were able to deliver safely only 800 mg daily in combination with 100 mg of oral etoposide. The dose-limiting toxicity was principally gastrointestinal, whereas myelotoxicity was mild (Table 3).

Although this study was performed to evaluate the toxicity, it has also been possible to assess the activity of this combination. The response rate of 13% was not particularly exciting. However, all our patients have been pretreated and were not responsive to a chemotherapeutic combination including cisplatin, epi-doxorubicin, leucovorin and 5-FU. Orally administered drugs are beneficial from the patient's point of view, because hospitalization is unnecessary. Furthermore, the possibility of administering chemotherapy safely at home can allow the treatment even of elderly patients, who represent the majority of gastric cancer patients.

In conclusion, our data show that etoposide and tegafur can be safely administered in combination by the oral route and that such a combination may have a therapeutic activity even in previously treated patients with advanced gastric carcinoma. Further phase II studies to confirm the activity and the safety of this combination seem to be warranted even in elderly patients.

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