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Short communication

Alternating chemotherapy in advanced gastric cancer

A phase II study

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Summary. A phase II study with an alternating chemotherapeutic scheme, in advanced gastric cancer was conducted. Twentytwo patients were treated with cisplatin and mitomycin C on day 1 and BCNU and doxorubicin on day 28. Tegafur p.o. was given daily from the start to the end of chemotherapy. This scheme was repeated every four weeks. Response rate was 25% (2 complete and 3 partial). However, remissions were short lived, and median survival for the entire group was 7 months. Haematological and gastrointestinal toxicities were severe. In conclusion, the low response rate and the high toxicity of this regimen preclude its use for the treatment of gastric cancer.

Introduction

Gastric cancer (GC) is relatively chemosensitive. In recent years, various combination chemotherapy regimens have been proposed, with responses varying from 42% with FAM (5-fluorouracil, adriamycin, mitomycin C) [4] to 62% with FAMtx (5-fluorouracil, adriamycin, methotrexate) [2] or 63% with EAP (etoposide, doxorubicin, cisplatin) [5]. However, the complete response (CR) rate with these regimens is hardly over 20%. For this reason it seems logical to develop newer therapeutic approaches and schemes in an attempt to obtain better results.

Based on the Goldy and Coldman hypothesis [1] and with the aim of preventing the early development of resistance that could preclude the attainment of CR, we decided to start a phase II study with an alternating chemotherapeutic scheme involving five drugs. This scheme consisted in the alternation of cisplatin, tegafur and mitomicin C with tegafur, doxorubicin and carmustine. The cisplatin, tegafur and mitomicin C combination was chosen on the basis of previously published reports showing the efficacy of a combination of mitomicin C and tegafur in GC [6]. The combination of cisplatin and 5-fluorouracil (5-FU) had also proven effective [3]. It therefore seemed reasonable to suppose that the use of these three drugs together might have an intensified antineoplastic effect. The use of tegafur, doxorubicin and carmustine in combination is a modification of the FAB protocol in which 5-FU is sustituted by tegafur in order to facilitate the administration of the regimen as an out-patient procedure. The results of this study are presented.

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Patients and methods

Patients with metastatic or inoperable, locally advanced and histologically confirmed GC were eligible. Bidimensionally measurable areas of malignant disease were also required. Patients had to be under 75 years of age and have a performance status of 0–3, an absolute granulocyte count in excess of 2000/l, platelet count 120×10^9/l, creatinine clearance in excess of 70 ml/min and serum bilirubin less than 40 mol/l. No patients who had received prior chemotherapy or radiotherapy were included. The therapeutic scheme was designed to allow administration on an out-patient basis. On day 1 cisplatin 100 mg/m^2 i.v., mitomicin C 10 mg/m^2 i.v. and tegafur 10 mg/kg p.o. were administered. Tegafur was then given daily at this dose until the end of chemotherapy. On day 28 the second part of the scheme was administered, i.e., BCNU 50 mg/m^2 and doxorubicin 40 mg/m^2, and daily tegafur was maintained. This scheme was repeated every 4 weeks.

It was decided to reevaluate patients after two courses of chemotherapy (day 84). If no response was found therapy was stopped; on the other hand, if a CR or a PR were found chemotherapy was continued for two more courses (to day 140).

The response criteria used were those of UICC, and toxicity was evaluated according to WHO criteria.

A total of 22 patients were enrolled in the study between April 1987 and December 1988, 2 of whom were not eligible for evaluation because they refused to comply after giving informed consent. Evaluable patient's characteristics are shown in Table 1.

Results

A response rate of 25% (2 CR and 3 PR) was observed, (95% confidence interval 5.7%–49.1%). The disease localizations in patients who achieved CR were liver and

Table 1. Patient characteristics

Male/female	15/5
Mean age (range) in years	53 (31–74)
Site of index lesion	
Liver	10
Pulmonary	6
Lymph node	3
Performance score (ECOG)	
0–1	9
2–3	11

lung. Reevaluation was performed with liver ultrasonography and thoraco-abdominal CT scan, respectively. The duration of response was 5 and 7 months in these two patients. The three patients with PR had liver metastases and response was evaluated by liver ultrasonography. Response duration was 3, 4 and 6 months. All but three patients have died. The overall median survival is 7 months.

All 20 patients were evaluable for toxicity. Grade 3 nausea/vomiting was presented in 12 and grade 4 in 3. Haematological depression was common, with grade 3 neutropoenia in 8 patients and grade 4 in 1. There were 3 patients with grade 3 thrombocytopoenia. Oral tegafur was frequently badly tolerated, 14 patients reporting epigastric pain and 3, diarrhoea (1, grade 2 and 2, grade 3). For this reason the dose of tegafur was reduced to 50% in 8 patients. Alopoecia grade 2 was observed in 12 patients and grade 3 in 4.

Discussion

The results of this study show that this regimen is moderately active in advanced GC. In fact, the response rate observed is quite similar to that described by several authors working with other cytotoxic combinations. However, these results are in the range of those obtained with single-agent therapy with any of the drugs used in this scheme.

These results could be partially atributed to tegafur toxicity, which necessitated a dose reduction in 40% of patients. However, it seems more reasonable to attribute them to the low efficacy of the regimens employed.

In conclusion, because of the low response rate and the high toxicity, this regimen cannot be recommended for the treatment of GC.

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