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## Short Communication

# Fotemustine in Patients with Advanced Gastric Cancer, a Phase II Trial From the EORTC-GITCCG (European Organization for Research and Treatment of Cancer, Gastrointestinal Tract Cancer Cooperative Group)

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Fotemustine activity was evaluated in 26 patients, mostly pretreated, with advanced gastric cancer. Its main toxicity was haematological with grade 3-4 neutropenia in 32% and grade 3-4 thrombocytopenia in 50% of the patients, complicated by 2 toxicity-related deaths due to haemorrhage. No complete or partial responses were observed in the 26 eligible patients and median survival was only 11 weeks. Fotemustine therefore has no activity in advanced gastric cancer. Copyright © 1996 Elsevier Science Ltd

**Key words:** fotemustine, gastric cancer, phase II trial

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### INTRODUCTION

ONLY A few single cytotoxic drugs are active in advanced gastric cancers (AGC): mainly 5-fluorouracil, cisplatinum and the anthracyclines. Their activity is relatively low, producing an objective response in around 20% of patients, and combinations of these drugs produce a maximum response rate of 40% or less in randomised trials [1]. As some activity has been reported for nitrosoureas [2], the EORTC-GITCCG launched a phase II trial of fotemustine (Murphoran®, ServierLab, France) a new nitrosourea [3], which has shown activity in advanced melanoma [4].

### PATIENTS AND METHODS

Fotemustine was administered as second-line therapy in patients with histologically proven AGC. Eligible patients were not to have had previous treatment with nitrosoureas and no more than one previous chemotherapy regimen. Lesions had to be bidimensionally measureable, located outside previously irradiated fields, and to have progressed within the last 2 months. The performance status (PS) requirement was grade < 3 (WHO grade), and blood counts, and liver and renal function tests had to be normal.

Fotemustine was given as a 30 min infusion at a dose of 100

mg/m<sup>2</sup>, on days 1 and 8 for patients having experienced haematological toxicity (WHO grade > 2) while on prior chemotherapy, and on days 1-8 and 15 for the others during the induction cycles [3]. After a rest period of 5 weeks, additional cycles of fotemustine were administered at the same dose but once every three weeks for three cycles and then every 6 weeks for three further cycles. Tumour response and toxicity were evaluated according to WHO criteria [5].

### RESULTS

*Population (Table 1)*

Of the 30 patients entered, 26 were considered eligible and 4 were ineligible (inadequate PS:1; more than one previous

Table 1. EORTC-GITCCG trial: population of patients with advanced gastric cancer treated with fotemustine

Characteristics	Number
Eligible patients (pts)	26/30
Sex (female/male)	3/23
Median age (years) (range)	56 (37-74)
Performance status (WHO grade)	
0-1	20
2	6
Pretreated/non-pretreated patients	25/1

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CT:1; insufficient blood count:2); of the 26 patients, 1 had never been treated. The median number of cycles administered was three (range 0–8) and the dose administered was  $100\% \pm 4\%$  of the scheduled dose for the initial part of the treatment.

#### Toxicity

Grade 3–4 haematological toxicity was observed in 32% of patients for white blood cells and in 50% for platelets during treatment. We also observed delayed haematological toxicity at weeks 5–7 after discontinuation of chemotherapy in the 12 evaluable patients with more than 35 days of follow-up after start of the treatment. Non-haematological toxicity was low: grade 2 and 3 vomiting in 24 and 16%, respectively, grade 1, 2 and 3 alopecia in 4, 4 and 8%, respectively, and general malaise or flu-like syndrome in 4 patients (16%). Two deaths were due to massive digestive haemorrhage from the tumour which was certainly related to grade 4 thrombocytopenia.

#### Responses

With WHO criteria, no objective responses were observed, but 4 patients had disease stabilisation for more than 4 weeks. In contrast, disease in 5 patients progressed very rapidly, and 1 died of tumour progression even before administration of fotemustine and another after the first cycle.

Treatment was discontinued due to tumour progression in 70% of the cases and because of toxicity in 8%. Treatment was interrupted in 1 patient because of pulmonary embolism. 1 patient was lost to follow-up.

Survival was short with a median of 11 weeks and a range of 10 days to 37+ weeks.

### DISCUSSION

Fotemustine exhibited no activity on advanced gastric cancer in this study, although most of the patients were, apparently, in good general condition. This may be related to the fact that all but 1 of the patients had been pretreated, thus emphasising how difficult it is to assess a new drug's activity for gastric cancer in a second-line setting; disease will progress in many patients very rapidly even before planned treatment, as was the case in 1 of our patients. Indeed, only 14/26 received 3 or more cycles of chemotherapy and only 1 received the full course of treatment (8 cycles). With no response in 14 patients, activity must be excluded in more than 15% of pretreated patients.

One of the reasons for such a lack of efficacy could be the

schedule used in this study. The 5-week rest period after induction treatment could promote tumour progression in these rapidly growing tumours. It is noteworthy that one of the most efficient chemotherapy protocols, the FAMTX protocol, administers chemotherapy every 2 weeks [6]. Thus, it cannot be excluded that another mode of administration (i.e. every 3 weeks) or combination with a non-haematotoxic drug could lead to activity in AGC, although previous trials using combination 5-FU and methyl-CCNU, another nitrosourea, yielded no significant activity [7, 8].

Although the true activity of fotemustine in untreated gastric cancer has yet to be demonstrated, fotemustine with this schedule has clearly not improved our therapeutic armamentarium in advanced gastric cancer. These results are unfortunately very similar to those observed with fotemustine and the same protocol in advanced colorectal cancer [9].

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