Eur J Cancer, Vol. 26, No. 1, pp. 63–65. 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Clinical Trial Summary

An EORTC Phase II Study of Sequential Methotrexate–Fluorouracil in Locally Advanced or Metastatic Gastric Cancer

GEERT BLIJHAM,*§ HARRY BLEIBERG,† NICOLE DUEZ‡ and MARC BUYSE‡ for the EORTC Gastrointestinal Cancer Cooperative Group

**Department of Internal Medicine, Division of Haematology–Oncology, Academic Hospital Maastricht, P.O. Box 1918, 6201 BX Maastricht, The Netherlands, †Institut Jules Bordet, 1 rue Héger Bordet, B-1000 Bruxelles, Belgium and ‡EORTC Data Center, 125 Boulevard de Waterloo, B-1000 Bruxelles, Belgium*

INTRODUCTION

OF THE gastrointestinal malignancies, gastric carcinoma is one of the most responsive to chemotherapy [1]. Despite encouraging response rates to various combinations, survival does not appear to be prolonged as compared to treatment with 5-fluorouracil (FU) alone [2]. Recently, Klein *et al.* developed a combination of high doses of methotrexate (MTX) and FU, followed after 14 days by a low dose of doxorubicin [3]. In an EORTC trial with this FAMTX regimen, 33 of 67 patients responded; toxicity in this and other studies, however, was considerable [4, 5] and may at least in part have been attributable to the high dose of MTX (1500 mg/m^2). We decided to further investigate the MTX–FU schedule in gastric cancer by employing a lower dose of MTX, which had been shown to improve results obtained with FU in metastatic colorectal cancer [6]. If active and of low toxicity, this schedule could be used for the addition of other active drugs.

PATIENTS AND METHODS

Patients with metastatic or inoperable locally advanced histologically proven gastric cancer were eligible. They should be less than 75 years of age and with a Karnofsky performance score of 60% or more. Other criteria included a creatinine clearance exceeding 70 ml/min, serum bilirubin less than 40 μmol/l, and leucocyte and platelet counts exceeding 4×10^9/l and 120×10^9/l respectively. Patients should have measurable disease, which included a hepatomegaly of more than 5 cm if proven to contain metastases and metastases seen by CT scan or echography, provided that the largest diameter of the lesion was at least 3 cm.

No prior chemotherapy or radiotherapy to indicator lesions was accepted.

Patients were treated with MTX, 150 mg/m^2 i.v. push, directly followed by MTX, 150 mg/m^2 in 500 ml isotonic saline i.v. over 4 h. Seven hours after the start of MTX, FU was given as 900 mg/m^2 i.v. push. Leucovorin was started as 22.5 mg (1.5 tablets) orally 24 h after MTX and continued at 6 h intervals for 48 h.

Before receiving MTX, patients were started on an i.v. infusion of 1.4% bicarbonate; MTX was started as soon as the urinary pH exceeded 7. Patients were to receive at least 3 l of fluid in the first 24 h and a diuresis of at least 100 ml/h had to be maintained.

The chemotherapy schedule was to be repeated every 2 weeks. New courses were given only if the leucocyte and platelet count exceeded 3×10^9/l and 100×10^9/l respectively. Treatment was continued for two courses after complete remission or till progression. Response criteria were according to UICC. The response was first evaluated just prior

Accepted 26 September 1989.
§To whom correspondence and requests for reprints should be sent.

to the 4th course. Toxicity was evaluated according to WHO criteria.

RESULTS

A total of 28 patients was registered between May 1985 and June 1986. Three patients were not eligible, one because of refusal after informed consent, one because no measurable disease was present and one because no data were received. Of the 25 evaluable patients, three were not evaluable for response. In two of these patients, intervals between courses greatly exceeded 2 weeks without toxicity reasons; one patient died because of an unknown cause at home after two courses. All evaluable patients are included in the calculation of survival; 22 fully evaluable patients were used for toxicity and response data. The characteristics are included in Table 1.

As far as responses are concerned, four patients showed early progression during the first three courses and nine others were progressing at the time of first protocol evaluation, that is just prior to the 4th course. Four patients developed a partial response (18%) with duration of 3, 4, 4 and 7 months. Two responses were documented by echography and occurred in the liver and (in one patient) also in regional nodes. One response, also in the liver, was documented by CT scan and one patient with primary tumor and large ovarian metastases showed a partial response upon relaparotomy.

Table 1. Sequential methotrexate and 5-fluorouracil in locally advanced or metastatic gastric cancer

Patient characteristics	
Number of patients (male)	25 (16)
Mean age (range)	49 years (31–70)
No prior surgery	11
Response	
Progression	13
No change	5
Partial response	4 (18%)
Median survival time	4 months

Median survival time with 19 of 25 patients expired was 4 months.

Toxicity was generally mild with grade 3 nausea/vomiting in three, diarrhea in one and alopecia in two patients. Although the great majority of patients experienced little or no myelosuppression, four patients developed grade 4 neutropenia; in three of these ascites or pleural fluid, though clinically insignificant, were found with imaging techniques. Although no toxic death occurred, one patient went through a life-threatening neutropenic septic episode.

DISCUSSION

With a response rate of 18%, this particular schedule of sequential MTX and FU administration most likely has no advantages over treatment with FU alone. Moreover, although the subjective toxicity was low, occasional episodes of severe and sometimes life-threatening neutropenia were observed. The occurrence of these episodes may be related to the presence of subclinical amounts of abdominal or pleural fluid.

The reasons for the relative failure of this particular combination are unknown. MTX, in the dose and schedule applied in this study, has been shown to improve results with FU in metastatic colorectal cancer [6]. In the same disease, Kemeny *et al.* showed even lower doses of MTX to be synergistic and provided evidence for intervals exceeding 3 h to be necessary to obtain this effect [7]. This raises the question whether the favorable response rate, obtained with FAMTX in gastric cancer, may be due to other mechanisms than those generally implied for synergistic MTX–FU combinations. The EORTC is currently conducting a comparative phase III study of FAMTX and FAM. If in this trial the superiority of FAMTX is confirmed, further studies on the mechanisms underlying this superiority may be in order.

Acknowledgements—We gratefully acknowledge the participation in this study of Drs Chemachovic (Hospital Erasme, Brussels), Planting (Dr Daniel den Hoed Hospital, Rotterdam), Neyt (Academic Hospital Utrecht), Malhaire (Centre de Brest, France), Conroy (Centre A. Vautrin, Nancy) and Herrmann (Universitätsklinikum, Berlin).

REFERENCES

1. O'Connell MJ. Current status of chemotherapy for advanced pancreatic and gastric cancer. *J Clin Oncol* 1985, **3**, 1032–1039.
2. Cullinan SA, Moertel CG, Fleming TR *et al.* A comparison of chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. *JAMA* 1985, **253**, 2061–2067.
3. Klein HO, Dias Wickramanayke P, Dieterle F *et al.* Chemotherapieprotokoll zur Behandlung des metastasierden Magenkarzinoms. Methotrexat, Adriamycin® und 5-Fluorouracil. *Dtsch Med Wochenschr* 1982, **107**, 1708–1712.
4. Wils J, Bleiberg H, Dalesio O *et al.* An EORTC Gastrointestinal Group evaluation of the combination of sequential methotrexate and 5-fluorouracil, combined with Adriamycin® in advanced measurable gastric cancer. *J Clin Oncol* 1986, **4**, 1799–1803.

5. Cunningham D, Gilchrist NL, Forrest GJ, Soukop M, McArdle CS, Carter DC. Chemotherapy in advanced gastric cancer. *Cancer Treat Rep* 1985, **69**, 927.
6. Herrmann R, Spehn J, Beyer JH *et al.* Sequential methotrexate and 5-fluorouracil: improved response rate in metastatic colorectal cancer. *J Clin Oncol* 1984, **2**, 591–594.
7. Kemeny NE, Ahmed T, Michaelson RA. Activity of sequential low-dose methotrexate and fluorouracil in advanced colorectal carcinoma: attempt at correlation with tissue and blood levels of phosphoribonylpyrophosphate. *J Clin Oncol* 1984, **2**, 311–315.