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Epirubicin, Cisplatin and Intermittent Continuous Infusion of 5-Fluorouracil in Advanced Gastric Cancer: an Effective Regimen?

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THE CYTOSTATIC drugs epirubicin, cisplatin and 5-fluorouracil (5-FU) have all shown activity in gastric cancer [1–3]. The response rates for these drugs are in the range of 19–36% [1–3]. Combination regimens with these drugs have shown substantial activity in gastric cancer with response rates from 27 to 44% [4–7]. Recently, Findlay and colleagues reported a further improvement in response rate by administering 5-FU 200 mg/m^2/day continuously for 21 weeks with eight 3-weekly cycles of epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 (ECF) [3, 8]. In this study, 133 patients were treated resulting in a response rate of 71%, with 11% complete responses [3,8].

Encouraged by their results, we recently started a trial. Patients were treated with a continuous infusion of 5-FU for 14 days at a dose of 200 mg/m^2/day via a portable infusion pump (Pharmacia CADD-PLUS); epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 were administered on day 1 of the continuous infusion of 5-FU. Courses were given every 4 weeks, with a maximum of six courses. In case of grade 3–4 toxicity (WHO), the dose of epirubicin and cisplatin was reduced by 25%.

Currently, 9 patients (6 male, 3 female) with advanced gastric cancer have entered the study. The median age was 55 years (range 20–67). 6 patients had locally advanced disease and proved irresectable at laparotomy, and 3 patients had already distant metastases (liver, colon, pelvis). All patients had a WHO performance status of 0–2, a leucocyte count of $\geq 4.0 \times 10^9$/l and a platelet count of $\geq 100 \times 10^9$/l. One patient pretreated with six twice-weekly courses of continuous infusion of 5-FU has not responded so far.

Patients were considered evaluable for response after at least two courses. All patients were considered evaluable for toxicity. Toxicity evaluation took place every 2 weeks, response evaluation every two courses. Patients with locally advanced disease were evaluated by computed tomography (CT) scan and/or endosonography or endoscopy; patients with metastases were evaluated with CT scan or ultrasound.

A total of 29 courses (median three, range two to six) was given; 98% of the planned continuous infusion days were completed. Some form of toxicity occurred in all patients (Table 1). Dose reduction was necessary in 2 patients because of grade 3 toxicity. All patients were evaluable for response. No objective responses were observed (RR 0%, 95% confidence interval 0–34%). 7 patients progressed after a median of three courses (range two to four). 2 patients had stable disease. One of these patients was again considered for surgery because of a remarkable subjective response. However, no curative resection could be performed.

Table 1. Toxicity according to the WHO criteria

Toxicity (n = 9)	Grade 1	Grade 2	Grade 3
Nausea/vomiting	4	3	2
Diarrhoea	3	0	0
Leucopenia	2	2	0
Mucositis	0	0	0

Data represent number of patients.

The preliminary results of our study indicate that the regimen of intermittent continuous infusion of 5-FU in combination with epirubicin and cisplatin every 4 weeks is not an active regimen. This is rather unexpected because all agents used in this regimen have shown activity as a single agent [1–3]. Furthermore, the combination of these three drugs is reported to result in a high response rate [4–7].

Our schedule differed from that of Findlay's in that we used a 4-weekly infusion of epirubicin and cisplatin and that 5-FU was administered intermittently. This may be the cause of our poor results and can be a warning that changing a schedule to a more convenient one for the patient may result in drastic changes in response rate. Our study also underlines the necessity to confirm the results of Findlay and colleagues before this regimen can be accepted as the standard treatment for advanced gastric cancer.

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