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Letters

Intermittent Continuous Intravenous Infusion of 5-Fluoruoracil; a Useful Approach in Disseminated Colorectal Cancer?

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5-FLUOROURACIL (5-FU) is still the only active drug in colorectal cancer with an average response rate of about 20% [1]. Recently some progress has been made by expanding the infusion time of 5-FU [1, 2]. Several trials of continuous infusion of 5-FU have been published using different infusion schedules [1, 3–9], reporting response rates in the range of 30–40%.

We performed a study with an intermittent schedule of continuous infusion. The main goal was to improve the therapeutic index by minimising toxicity while retaining the response rate on a standard dose of 5-FU.

Between March 1990 and January 1992, 23 patients (14 male, 9 female) with metastatic colorectal cancer were entered into the study. The median age was 57 years (range 35–75). All patients had progression of measurable disease. 17 patients had liver, 4 patients lung, 1 patient peritoneum and 1 patient abdominal wall metastases as indicator lesions. All patients had a WHO performance status of 0–2, a leucocyte count of $\geq 4.0 \times 10^9/l$, a platelet count of $\geq 100 \times 10^9/l$, and had no previous chemotherapy.

Patients were treated with continuous infusion of 5-FU for 14 days at a dose of 300 mg/m²/day via a portable micropump (Parker). After a 2-week interval, the next course was given. In case of disease progression the dose of 5-FU was escalated by 25% until toxicity every two courses. If grade 3 or 4 toxicity occurred at the 5-FU dose of 300 mg/m²/day, the 5-FU dose was reduced by 25%.

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. Objective response and toxicity were defined according to standard WHO-criteria.

4 patients were not evaluable for response: 1 patient discontinued treatment because of grade 3 toxicity; 3 patients had early progression. 19 patients were evaluable for response. 2 patients (11%, 95% confidence interval 1–33%) had a partial response (15 and 21+ months); 5 patients had progressive disease after two courses and 12 patients had stable disease for a median duration of 5.5 months (3–16 months). Dose escalation was eventually given in 11 patients, with no additional effect. Median survival of the whole group was 10 months (2–22+ months).

Table 1. Toxicity according to the WHO criteria (5-FU 300 mg/m²/day)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	5	0	0	0
Mucositis	5	0	2	0
Diarrhoea	3	2	0	0
Skin	0	1	0	0
Haematological	0	0	0	0

Data represent the number of patients.

Some form of toxicity occurred in 52% of the patients, mainly grade 1 or 2 (see Table 1). In 2 patients treatment was stopped because of grade 3 toxicity. A dose reduction of 25% because of toxicity was necessary in 2 patients. 1 patient had a fatal acute myocardial infarction at the start of the sixth course.

Continuous infusion is feasible on an outpatient basis and easily accepted by the patients. No major technical problems were encountered during the whole period. The response rate of 11% in our study is, however, disappointingly low when compared with other reported continuous infusion studies [1, 3–9]. Although toxicity was mild, some form of toxicity was noted in the majority of patients and, therefore, an intermittent 14 days continuous infusion of 5-FU does not result in an improvement of the therapeutic index. The shortening of the infusion time led to a reduced toxicity, but at the same time to a decreased response rate, so intermittent continuous infusion offers no benefit as to the more prolonged infusion times.

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