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# Weekly High-dose Infusion of 5-Fluorouracil in Advanced Colorectal Cancer

**E. Diaz-Rubio, E. Aranda, M. Martin, R. Gonzalez-Mancha, J. Gonzalez-Larriba and I. Barneto**

**18 patients with advanced colorectal cancer entered a phase I–II study of high-dose 48 h continuous infusion 5-fluorouracil (5-FU) for 6 weeks. 7 patients were included at the first dose level (3 g/m²) and only 1 had serious toxicity (grade 3 diarrhoea and mucositis). 7 patients were included at the second dose level (3.5 g/m²). 6 had a good tolerance to treatment, while the remaining patient had grade 4 leukopenia. 4 patients received 4 g/m²: 3 had severe toxicity (grade 4 diarrhoea, myelosuppression, mucositis, central nervous system), such that the entry of new patients was stopped. Anti-tumour activity was seen in 33% (95% confidence interval 13–59%) of the overall population. Only patients who had not had previous chemotherapy responded to treatment (response rate in this subgroup [43%, 18–71%]). The optimal dose of 5-FU was 3.5 g/m² weekly for six cycles.**
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## INTRODUCTION

5-FLUOROURACIL (5-FU) is the most widely used cytotoxic drug in advanced colorectal cancer. However, its anti-tumour activity is below 20% [1]. Several studies have suggested that continuous infusion may increase response rate and tolerance to treatment [2–5]. A weekly 48 h continuous infusion of high-dose 5-FU (60 mg/kg) had little toxicity [3, 6]. Therefore, we have done a phase I–II study of escalating doses of weekly 48 h continuous infusion of 5-FU to determine the optimal dose of this schedule and to evaluate the response rate.

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## PATIENTS AND METHODS

Patients had advanced colorectal cancer, with or without previous chemotherapy. Other inclusion criteria were Karnofsky status above 70%, age under 75 years, life expectancy of at least 2 months, white cell count over 4000/μl, platelet count over 150,000/μl, bilirubin below 1.5 mg/dl and creatinine less than 1.2 mg/dl.

18 patients entered the study (Table 1). After informed consent was obtained, patients received the total dose of 5-FU administered in 2000 ml normal saline over 48 h as an inpatient. The solution was protected from the light. Chemotherapy was repeated weekly for six doses except when toxicity was severe. The initial dose we used was 3 g/m². Subsequently, we used 3.5 g/m² in other patients, and then 4 g/m² in the final group of patients.

Toxicity and response to therapy were defined with WHO criteria [7]. During treatment, the following tests and examinations were done: physical examination (twice a week), white

*Table 1. Patients' characteristics*

| | |
|---|---|
| No. of patients | 18 |
| Previous chemotherapy | 4* |
| M/F | 10/8 |
| Median age (range) | 60 (46–68) |
| Median Karnofsky index (range) | 90 (80–100) |
| Site of primary tumour | |
| Colon | 8 |
| Rectum | 10 |
| Sites of disease | |
| Local abdominal/pelvic mass | 9 |
| Liver | 13 |
| Lung | 3 |
| Peritoneum | 2 |

*Including Tegafur in 2 cases, cisplatin plus 5-FU in 1 case and BCNU plus 5-FU in 1 case.

*Table 2. Toxicity*

| Side-effect (grade) | Dose (g/m²) 3 ($n$ = 7) | 3.5 ($n$ = 7) | 4 ($n$ = 4) |
|---|---|---|---|
| Leukopenia | | | |
| 4 | 0 | 1 | 1 |
| Thrombocytopenia | | | |
| 4 | 0 | 0 | 1 |
| Mucositis | | | |
| 1 | 2 | 1 | 0 |
| 2 | 2 | 3 | 2 |
| 3 | 1 | 0 | 0 |
| 4 | 0 | 0 | 1 |
| Emesis | | | |
| 1 | 1 | 2 | 1 |
| 2 | 3 | 3 | 1 |
| Diarrhoea | | | |
| 1 | 1 | 1 | 1 |
| 2 | 0 | 1 | 0 |
| 3 | 1 | 0 | 0 |
| 4 | 0 | 0 | 2 |
| Alopecia | | | |
| 1 | 1 | 0 | 1 |
| Skin toxicity* | | | |
| 1 | 1 | 0 | 1 |
| 2 | 0 | 0 | 2 |
| Phlebitis† | 2 | 2 | 1 |
| CNS toxicity | | | |
| 3 | 0 | 0 | 1 |

*3 patients had a plantar erythrodysesthesia syndrome and 1 a rash.
†5-FU was infused via a peripheral vein in all patients.
CNS = central nervous system.

and red cell and platelet count (twice a week), measurement of aspartate and alanine aminotransferase, creatinine, alkaline phosphatase, lactate dehydrogenase and electrolytes (once a week) and examination necessary for response evaluation (before and after the 6 week period of treatment).

## RESULTS

7 patients received 3 g/m². 6 completed the planned therapy without any serious toxicity, but 1 received four doses only due to grade 3 diarrhoea and mucositis (Table 2).

7 patients received 3.5 g/m². 1 patient had grade 4 leukopenia after the second week of 5-FU and treatment was stopped. The other 6 patients showed a good tolerance to treatment. Finally 4 patients were given 4 g/m². Toxicity in 3 was severe, so the entry of new patients was stopped. Only 1 patient at this dose level was able to complete the planned 6 weeks of therapy. The other 3 patients stopped treatment due to toxicity. 2 had grade 4 diarrhoea, while the remaining patient had grade 4 leukopenia, thrombocytopenia and mucositis, as well as disorientation, irritability and confusion. Computed tomography of the brain and cerebrospinal fluid examination did not reveal any abnormality. This patient recovered from haematological toxicity but had a lung collapse due to accumulation of bronchial secretions. He died despite bronchoscopic aspiration. All patients included at the highest dose levels were previously untreated.

One complete (6%) and 5 partial (28%) responses were observed among the 18 patients (overall response rate 33%, 95% confidence limits 13–59%). Only patients who had not had previous chemotherapy responded to treatment. The overall response rate in this last group of patients was 6/14 (43%, 95% confidence limits 18–71%). Responses were seen in the lung (1 case), liver (1) and liver plus pelvis (2). The median duration of responses was 6.5 months.

## DISCUSSION

Despite the high number of studies with 5-FU in advanced colorectal cancer, we still do not know the best schedule. With the classical 5 day bolus schedule, the dose-limiting toxicity of the drug was myelosuppression [8, 9]. An 8 h continuous infusion induced less toxicity, although at the expense of reduced response rate [10]. Various continuous infusion schedules (48 h, 5 days or more protracted schemes) may increase the response rate with a simultaneous decrease in toxicity [2–5]. A weekly 48 h continuous infusion of high doses (60 mg/kg) was well tolerated [3, 6].

From our study, the optimal dose of weekly 5-FU in a 48 h continuous infusion was 3.5 g/m². 3 out of 4 patients at the next dose level (4 g/m²) had severe toxicity, which forced us to stop the entry of new patients. Diarrhoea and myelosuppresion were the dose-limiting toxicities of this schedule of administration of 5-FU. The response rate obtained in our study was encouraging, with 6 out of 18 objective responses (33%) in the overall population and 6 out of 14 (43%) in previously untreated patients. However, only 7 patients were included at a dose of 3.5 g/m². Hence, this is not a large enough sample of patients to make a definitive statement about response.

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# Effect of Cyclophosphamide Pretreatment on Daunorubicin in Rat Acute Leukaemia Model

**Kees Nooter, Arjan de Vries, Anton C.M. Martens and Anton Hagenbeek**

**The total number of leukaemic cells at the time of therapy may affect the tissue and target cell distribution and antitumour efficacy of cytotoxic drugs. The effects of low dose cyclophosphamide pretreatment on daunorubicin concentrations in leukaemic bone marrow were investigated in rats. At day 12 after transplantation of the leukaemia, rats were injected intraperitoneally with cyclophosphamide (30 mg/kg). 2 days later the leukaemic rats received daunorubicin intravenously (7.5 mg/kg). Cyclophosphamide pretreatment led to a significant increase in daunorubicin concentration in the femoral bone marrow, by a factor of about 7. The log leukaemic stem cell kill (LCK) values, as estimated by a survival assay, were 1.8, 0.7, and 5.4 for the leukaemic rats injected with cyclophosphamide (day 12), with daunorubicin (day 14), or with cyclophosphamide (day 12) plus daunorubicin (day 14), respectively). The simultaneous administration of cyclophosphamide and daunorubicin at day 14, induced a LCK of 2.7, a value that was the sum of the LCKs of cyclophosphamide and daunorubicin alone. Low-dose cyclophosphamide pretreatment led to an increased daunorubicin accumulation in femoral bone marrow of leukaemic rats, and was synergistic with daunorubicin.**
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## INTRODUCTION

IN MOST leukaemic patients some leukaemic stem cells survive current chemotherapies [1]. Theoretically, the surviving tumour cells can endure higher drug concentrations and resist treatment. However, no unifying biochemical mechanism has been identified yet, in leukaemias, that makes the cells drug resistant. The high relapse rate in patients with acute myelocytic leukaemia (AML) may also be explained by the surviving tumour cells being exposed to inappropriate drug concentrations. Indeed, in the Brown Norway rat (BNML) model, we found that femoral bone marrow accumulated less daunorubicin than normal bone marrow, especially at the stage of high leukaemic cell burden [2]. Daunorubicin, with its high affinity for cellular DNA, may be rapidly taken up and retained by the easily accessible leukaemic cells. Removal of a large mass (about 1 g) of leukaemic cells by splenectomy resulted in partial restoration of the reduced drug uptake by femoral bone marrow. Using the same animal model for human AML, we have been working on chemoreduction of tumour load before the start of the 'real' chemotherapy.

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## MATERIALS AND METHODS

### *Chemicals*

Daunorubicin, daunorubicinol, and doxorubicin were donated by Farmitalia. Cyclophosphamide was obtained from