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High Dose 5-Fluorouracil (5-FU) and Folinic Acid in Advanced Colorectal Cancer Resistant to Standard Dose 5-FU Treatment: Results of a Phase II Study

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THE COMBINATION of 5-fluorouracil (5-FU) with folinic acid (FA) is considered to be the standard first-line treatment for metastatic colorectal cancer, with response rates of 20–30% [1, 2]. Patients resistant to standard dose single-agent 5-FU therapy may benefit from dose escalation of 5-FU as preliminary results in heterogeneously pretreated patients suggest [3–7]. To evaluate the toxicity and therapeutic effect of high dose 5-FU/FA, we conducted a phase II trial in patients who had been pretreated with a weekly standard dose of 5-FU within a randomised multicentre study, comparing high dose FA with low dose FA combined with standard dose 5-FU in 300 evaluable patients [2].

Patients with progressive disease under treatment with weekly 5-FU 500 mg/m^2 combined with either 500 or 20 mg/m^2 FA were enrolled according to standard eligibility criteria. 5-FU 2.600 mg/m^2 was administered as a 24 h infusion after a 1 h infusion of 500 mg/m^2 FA weekly via an intravenous port catheter system.

Patients were treated until tumour progression was documented. In case of tumour regression, treatment was limited to 4 weeks after achieving a complete or partial response or disease stabilisation. Therapy was restarted with documented tumour progression after treatment interruption.

From June 1992, 64 consecutive patients were enrolled. Patients' characteristics are presented in Table 1. All patients had previously received 5-FU treatment until disease progression. Patients with tumours progressing during treatment-free intervals were first restarted on their prior chemotherapy regimen until progression under treatment occurred.

A total of 663 high dose 5-FU infusions (median 10.3/case) were administered. A partial response was observed in 16/64 patients (25%) and the median duration of partial response was 6.9 months. 39/64 (61%) patients experienced disease stabilisation with a median time to progression of 3.5 months. 9/64 (14%) patients had progressive disease. Tumour-related pain improved significantly in 31/36 patients. Median survival time was 8 months (range 1–26), for patients with partial response 11 months (range 3–19+), and for patients with progressive disease 3 months (1–5). A positive correlation with survival was found in patients with a small number of metastatic sites (less than two), absence of peritoneal disease, complete response, partial response or stable disease under prior treatment and partial response under present treatment.

Table 1. Patients' characteristics (n = 64)

	No. of patients
Female/Male	16/48
Median age (years)	57 (range 30–71)
Karnofsky	70
Primary tumour	
Rectum	18
Colon	46
Sites of disease	
Local	19
Liver	48
Lung	17
Lymph nodes	26
Peritoneum	11
Bone	1

Overall toxicity was moderate. No WHO grade IV toxicity was observed. WHO grade III diarrhoea was observed in 7 patients, WHO grade III mucositis in 5 patients, WHO grade III nausea in 5 patients, WHO grade III hand–foot syndrome in 9 patients, and WHO grade III leucopenia in 2 patients.

For colorectal cancer, refractory to standard dose 5-FU, there is currently no second-line treatment recommended. High dose 5-FU, however, has been demonstrated to be active in patients who have failed other low dose 5-FU-based schedules. In this study, we achieved a response rate of 25% and a median survival time of 8 months with moderate toxicity. High dose 5-FU/FA is a well tolerated second-line treatment regimen for advanced colorectal cancer, refractory to standard dose 5-FU. Moderate toxicity combined with remarkable remission rates, considering the 5-FU pretreatment, effective control of tumour-related symptoms, prolonged progression-free intervals and prolonged survival contribute to an effective palliation. High dose 5-FU/FA is recommended as a second-line regimen after standard dose 5-FU pretreatment.

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