

Continuous Infusion 5-fluorouracil as Salvage Chemotherapy in Patients with Advanced Colorectal Cancer

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Abstract

For almost 40 years, 5-fluorouracil (5-FU) has been the only useful drug with clinically meaningful activity in metastatic colorectal carcinoma. When the disease progresses or recurs despite bolus 5-FU treatment, the options are limited. Our study shows that 5-FU given by continuous infusion is a viable alternative. Fifty-three patients received continuous infusion 5-FU. The overall response was 9%. Median survival of the entire cohort was 5 months. Patients with partial response and stable disease had median survival duration of 8 and 9 months, respectively. A dose-response relationship was observed. The commonest toxicities were mucositis (34%) and palmar-plantar syndrome (24%). There was no central line-related complication. Continuous infusion 5-FU is an effective "second-line" treatment. Further work is needed to ascertain its role, in comparison with newer agents like irinotecan (CPT-11), and oxaliplatin.

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Key words: Bolus 5-fluorouracil, Dose intensity, Palmar-plantar syndrome, Second-line chemotherapy, Toxicity

Introduction

Studies have shown beyond doubt that chemotherapy for metastatic colorectal cancer prolongs survival, impedes progression and stabilises disease.^{1,2} Compared with supportive care alone, it could also provide considerable benefits in terms of improved quality of life. However, what constitutes the standard palliative chemotherapy for advanced colorectal cancer has been the subject of controversy. While there is some indication that modulated 5-fluorouracil and continuous infusion 5-FU (CI 5-FU) may yield better tumour response than the same drug given in bolus schedules, there has been no statistically significant difference in overall survival in several large studies.³⁻⁶ Hence on the grounds of convenience, bolus 5-FU regimens have remained the mainstay of treatment of advanced colorectal cancer.

When tumour becomes refractory to bolus 5-FU, CI 5-FU has been used with some response. *In vitro* studies showed that tumour cells resistant to bolus 5-FU can still be sensitive to CI 5-FU. There is a lack of cross-resistance between these dosing schedules, and 5-FU appears to function as 2 different drugs depending on the mode of administration.⁷⁻¹⁰ Conventional bolus dosing results in peak plasma concentrations followed by a rapid decline,

with a half-life of 6 to 20 minutes. Cytotoxic effects are thus maintained for only a few hours. Continuous infusion 5-FU increases the time of exposure of the tumour cells to drug, resulting in growth inhibition through its effect on thymidylate synthetase, thus enhancing cell death. This has implications on its use as "second-line" chemotherapy for colorectal cancer.

Our study described the use of CI 5-FU as "second-line" chemotherapy for advanced colorectal cancer, which had failed initial chemotherapy with a bolus 5-FU regimen.

Patients and Methods

Patient Selection

Patients on follow-up treatment in our oncology clinic between October 1995 and January 1997 were accrued into the study. All of them had histology-proven metastatic colorectal cancer which were bi-dimensionally measurable. Biopsy of metastatic lesion was not required. Measurable disease was defined as a lesion measurable in two dimensions by computed tomography, ultrasound, or chest X-ray. They were ambulatory with good physical performance status [Eastern Cooperative Oncology Group (ECOG) performance score of 0

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to 2]. Renal and hepatic functions based on baseline serum creatinine and liver function tests were satisfactory: normal serum creatinine level, liver enzymes less than 2 times upper limit and bilirubin less than 1.5 times upper limit of normal range. All patients had received and discontinued bolus 5-FU based regimens because of disease progression. Some patients received radiotherapy to the primary site after surgery but not the metastatic lesion in study. Patient characteristics are outlined in Table I.

TABLE I: PATIENT CHARACTERISTICS

	n (%)
Sex	
Male	27 (50.9)
Female	26 (49.1)
Median age (years)	57
ECOG status	
1	34 (64.2)
2	19 (35.8)
Primary tumour	
Colon	33 (62.3)
Rectum/Rectosigmoid	20 (37.8)
Site of measurable lesion	
Liver	29 (54.7)
Lung	17 (32.0)
Lymph node	2 (3.8)
Peritoneum	4 (7.6)
Recurrence at primary site	1 (1.9)
Previous chemotherapy	
5-FU + FA	43 (81.2)
5-FU + levamisole	4 (7.5)
5-FU + FA + IFN	2 (3.8)
Other 5-FU regimens	4 (7.5)

5-FU: 5-fluorouracil; ECOG: Eastern Cooperative Oncology Group; FA: folinic acid; IFN: interferon

ECOG status: 0-asymptomatic; 1 -symptomatic, fully ambulant; 2-symptomatic, ambulant >50% waking hours; 3-symptomatic, in bed >50% waking hours; 4-symptomatic, confined to bed

Treatment

CI 5-FU was delivered by a Hickman central venous catheter using a portable infusion pump. Treatment was started with 5-FU at 200 mg/m²/day. Dose adjustments were made based on toxicities and disease progression. There was no interval between dosing. In the absence of significant toxicity, doses were increased gradually in increments of 10% after each review. Treatment was discontinued if patients developed significant toxicity or disease progression.

Response and Toxicity Assessment

The primary end-point of the study was objective tumour response. Response was assessed radiologically.

Patients were reviewed every 3 to 4 weeks. Radiological tumour assessments were made every 6 to 8 weeks using CT-scans or chest X-rays. Complete response was defined as complete disappearance of all lesion. Partial response required at least 50% reduction in the sum of all bi-dimensionally measurable tumour size. Stable disease was defined as reduction of tumour size by less than 50%, or an increase in tumour size of less than 25%. Progression status was assigned when there was increase in existing lesions by more than 25% or development of new lesions. Toxicities are defined using the World Health Organisation criteria. The duration of response was calculated from the point of entry into this study until development of disease progression or dose-limiting toxicity. Survival was calculated from the start of CI 5-FU to date of death or last follow-up. At each follow-up visit, detailed questioning of symptoms and physical examination was performed. The patients' body weights were charted, and weight loss of more than 10% was considered significant. Laboratory tests included full blood count every 3 to 4 weeks, and liver function tests every 6 to 8 weeks.

Results

Response

Fifty-three patients with metastatic disease were entered into the study. The overall response rate was 9%. There were no complete responders. Five patients were partial responders (9%), and 13 patients had stable disease (24%). Thirty-five patients had progressive disease (66%). Median duration of response was 5 months (range 2 to 14 months). Median duration of stable disease was 4 months (range 2 to 12 months). Results are detailed in Table II.

Toxicities

The toxicities observed in this study are illustrated in Table III. The most common toxicities were mucositis (34%) and palmar-plantar syndrome (28%). One patient had to terminate treatment because of severe palmar-plantar syndrome and mucositis. Grade 1 and 2 diarrhoea were seen in 15% of patients, and 1 required admission to hospital for Grade 4 diarrhoea. Mild nausea and vomiting were observed in 6% of patients. However, anti-emetics were not required. Seventeen per cent of patients noted anorexia. Leukopenia was not

TABLE II: RESPONSE RATE

	Colon	Rectum/Rectosigmoid
Complete response (CR)	0	0
Partial response (PR)	3	2
Stable disease	11	2
Progressive disease	19	16
Overall (CR+PR)	3	2

TABLE III : TOXICITY

Grade (WHO)	1	2	3	4
Mucositis	11		3	0
Diarrhoea	3	2	2	1
Nausea/vomiting	3	0	0	0
Palmar-plantar syndrome	12	2	1	0
Leukopenia	0	0	0	0

observed. Twenty-five patients (47%) tolerated CI 5-FU very well and did not develop documented toxicity.

Dose of CI 5-FU

The starting dose of 200 mg/m²/day was easily tolerated. Patients who did not develop significant adverse event had dose escalation after each review. The highest dose attained was 400 mg/m²/day. The mean dose for partial responders and patients with stable disease was 292 ± 63 mg/m²/day. This was comparatively higher than the mean dose seen in non-responders, 251 ± 40 mg/m²/day ($P < 0.01$).

Survival

All patients had died at the time of this report. The median survival of the entire cohort was 5 months. The median survival of patients who were partial responders was 8 months (range 3 to 26 months), for stable disease 9 months (range 3 to 42 months). The median survival of non-responders was 3 months (range 1 to 37 months). The survival curves are illustrated in Figure 1.

Discussion

Despite recent advances in cancer chemotherapy, 5-FU refractory disease continues to pose a therapeutic challenge to oncologists. Several new agents with some activities have emerged over the last few years. These include agents like irinotecan (CPT-II), oxaliplatin and thymidylate synthetase inhibitors. However such modest gains are often obtained at a cost of significant

toxicity and financial burden. The issues of toxicity and cost are important determinants in patients whose life-span is limited.

In such a situation, CI 5-FU appears to be a reasonable option. Several reports using CI 5-FU as second-line chemotherapy showed that 10% to 15% of patients having failed bolus 5-FU, achieved partial response to CI 5-FU regimes and another 20% achieved disease stabilisation that lasted as long as a partial response.^{11,12} In this study, the overall response rate was 9%, and disease was stabilised in 24%. The median duration of survival of patients with stable disease was comparable to that of a partial response. This is a meaningful observation because stable disease is a clinically beneficial effect of chemotherapy.^{12,13} Patients reported an improvement in symptoms, although "quality of life" was not formally assessed in this study. The median survival was longer for partial responders and patients with stable disease, than for non-responders. However this difference was not statistically significant. Thirty-three per cent of patients who had primary disease in the colon had stabilisation of disease as compared to 10% of patients with rectal or rectosigmoid cancer. This difference is significant, and warrants further study, as it could influence the use of CI 5-FU in patients with advanced rectal disease.

A linear dose-response relationship has been reported with CI 5-FU.¹⁴⁻¹⁶ At the same time, toxicity of 5-FU is generally dose-dependent. Compared to bolus schedules, higher 5-FU dose intensity could be achieved using continuous infusion without increase in toxicity.^{12,17} This is in concordance with our observation that the mean dose used was higher in responders than non-responders.

Toxicity profile of CI 5-FU is different from that of bolus regimes.^{4,5,11,12,18,19} There is a marked lack of leukopenia and a predominance of palmar-plantar syndrome reported. These observations are borne out in this study where the primary toxicities are palmar-plantar syndrome (28%) and mucositis (34%). The majority of toxicities observed were Grade 1. About half of our patients tolerated CI 5-FU extremely well with no documented toxicity. In patients who experienced more severe side-effects, the toxicities resolved after stopping 5-FU for 1 to 2 weeks. Most of the patients were able to continue 5-FU infusion, albeit at a lower dose. The toxicity of CI 5-FU was thus tolerable, and reversible when therapy was stopped. Only 1 patient required admission for diarrhoea, and 1 patient terminated treatment because of Grade 3 mucositis and palmar-plantar syndrome. Anorexia was reported in 9 patients, although this was never debilitating. None of the patients had significant weight loss. This favourable toxicity profile contributes significantly to preserving quality of life in these patients with advanced disease.

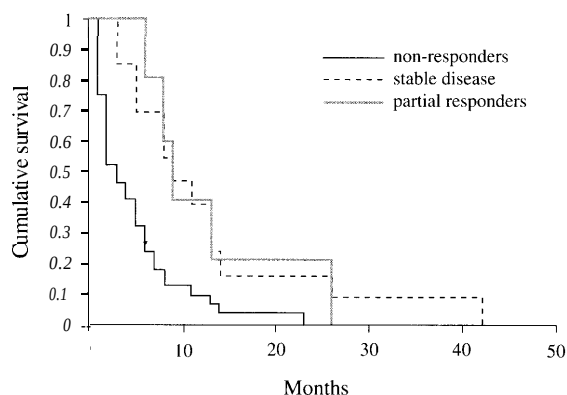


Fig. 1. Survival curves of patients treated with continuous infusion of 5-fluorouracil.

Lokich et al highlighted the potential practical problems of a protracted infusion and patient compliance. We find that with patient education and the use of newer generation infusion pumps, line-related complications can be kept to a minimum. Patients remained ambulatory and were able to leave home with the continuous infusion. They only had to return once a week for refill or dose adjustment. The use of this regimen hence had little effect on the patient's daily activities.

CI 5-FU is an acceptable salvage regimen for patients with disseminated colorectal cancer. The results of our study are encouraging. Further study is needed to compare CI 5-FU with current second-line regimens e.g. CPT-11 and oxaliplatin, in terms of objective response, clinical benefit response, toxicity, cost and their impact on quality of life.

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