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CLINICAL TRIAL REPORT

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Multimodal biochemical modulation of 5-fluorouracil by leucovorin, methotrexate, and interferon alpha in patients with advanced colorectal cancer

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Abstract A total of 26 patients with advanced colorectal cancer received 60 mg/m² methotrexate i.v. on days 1–4; 400 mg/m² 5-fluorouracil i.v. on days 2, 3, 5, and 6; and 100 mg/m² 6S-leucovorin i.v. on days 2, 3, 5, and 6. Interferon-α2b at a dose of 3 million U was given i.m. daily for the 6 days of chemotherapy. Courses were repeated every 3 weeks. There were four partial responses for a response rate of 15% (95% confidence interval 2–28%). In all, 14 patients expressed grade 3 toxicity; 9 patients had diarrhea, 3 had stomatitis, and 2 developed leukopenia. In conclusion, multimodal biochemical modulation of 5-fluorouracil, at least on this schedule, does not seem to be effective, as it results in severe toxicity.

Key words Colorectal cancer · 5-FU · Biochemical modulation

Introduction

Because of the limited success of 5-fluorouracil (5-FU) in controlling metastatic disease there has been much interest in the possibility of modulating its antitumor activity through different agents [1]. The rationale for the association between leucovorin (LV) and 5-FU arises from the possibility of increasing the inhibition of thymidylate synthase [1]. However, although this combination can actually be considered the most common regimen for the treatment of advanced colorectal cancer, only 15–20% of patients achieve an objective response with no well-defined advantage in survival [2]. Concerning 5-FU modulation with methotrexate (MTX), inhibition of dihydrofolic reductase produces a depletion of reduced folates. This state partially counteracts the potentiating effects caused by enhanced 5-FU metabolism secondary to the accumulation of pyrophosphatases [1]. However, a response rate of only about 20% is achievable with the combination of MTX and 5-FU [3]. In vitro studies have suggested synergy between 5-FU and interferon (IFN), also providing a possible mechanism of biochemical interactions. These include effects at the level of the target enzyme thymidine synthase on the uptake of thymidine and on thymidine kinase and phosphorylase [4]. Despite the preclinical and initially encouraging results of pilot studies, a randomized clinical trial has shown an activity similar to that achievable with the 5-FU/LV combination [5].

Because of the disappointing results obtained with single modulations and since biochemical modulations of 5-FU by LV, MTX, and IFN act in different sites and via different mechanisms, a pilot clinical trial was initiated to determine whether a triple biochemical modulation of 5-FU would be feasible and effective in advanced colorectal cancer.

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Patients and methods

Patients with histologically proven advanced and/or metastatic colorectal carcinoma not amenable to surgical resection were eligible for this study. Other eligibility criteria included no prior chemotherapy or irradiation; bidimensionally measurable disease; an expected survival of at least 3 months; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and adequate hepatic, renal, hematological, and cardiac functions. The treatment consisted of MTX given i.v. at 60 mg/m² on days 1–4; 5-FU given i.v. at 400 mg/m² on days 2, 3, 5, and 6; and 6S-LV given i.v. at 100 mg/m² on days 2, 3, 5, and 6. IFN-α2b at a dose of 3 million U was injected i.m. daily for the 6 days of chemotherapy. Courses were repeated every 3 weeks. Patients received acetominophen (500 mg given p.o. 1 h before IFN) to reduce IFN-induced toxicity. Response criteria and toxicity were assessed according to standard WHO criteria [6]. Tumor measurements were performed every three courses of therapy. All patients who received at least one cycle were evaluable for toxicity; to be considered evaluable for response, patients had to complete three cycles of chemotherapy.

A two-stage design was followed for this study such that the trial could be stopped early if the combination was inactive in this group of patients (response rate of $<20\%$). A total of 18 patients were initially entered; if one or more responses were observed, an additional 8 patients were entered. The chance that the trial would be stopped early (i.e., no response in the first 18 patients) was less than 4% if the true response rate was at least 20% [7]. Informed consent was obtained from all participants after the nature of the study had been fully explained.

Table 1 Patients' characteristics

Number of patients/evaluable	26/26
M/F	12/14
Age (years):	
Median	62
Range	30–75
Performance status (ECOG):	
0	10
1	12
2	4
Primary tumor site:	
Colon	17
Rectum	9
Location of confirmed metastases:	
Liver	8
Liver as major site	7
Lung	4
Local recurrence	5
Peritoneum	9

Results

A total of 26 patients were included in this clinical trial. Demographic characteristics recorded for the entire cohort are shown in Table 1. All patients were assessable for response and toxicity. There were four partial responses (three in the lung and one in the liver) for a response rate of 15% (95% confidence interval 2–28%). The duration of the responses were 4, 4, 4, and 6 months, respectively. The overall median survival was 10 months. In all, 14 patients experienced grade 3 toxicity; 9 patients had diarrhea, 3 had stomatitis, and 2 developed leukopenia. Five patients complained of fever of >38 °C after the first injection of IFN.

Discussion

The present schedule was designed on the basis of experimental data and previous clinical trials on biochemical modulation of 5-FU. MTX was given 24 h before 5-FU to maximize its effects on 5-FU, and a low dose was chosen on the basis of results reported on Kemeny et al. [8, 9]. IFN-α2b was given at a cyclic low dose according to preclinical and clinical data [4, 10, 11, 12]. Despite, these premises, the use of this regimen led to a disappointing response rate of 15%. The confidence interval (2–28%) overlapped those obtained with LV/5-FU or MTX/5-FU combinations [2, 3]. These results, together with the observed toxicity, led us to stop the trial.

Since our patient population was only minimally symptomatic and had a median performance status of 1, the poor response rate and side effects encountered in this trial probably do not reflect poor prognostic factors. On the other hand, some recent attempts at multiple modulation of 5-FU by IFN and LV failed to show any advantage [13, 14]. Furthermore, a recently published article on double biochemical modulation of 5-FU by high-dose LV and MTX failed to show any advantage in comparison with a single biochemical modulation [15].

In conclusion, multimodal biochemical modulation of 5-FU, at least on this schedule, does not seem to be effective. Because of the presence of toxicity, further clinical studies should be performed only after a better definition has been reached in preclinical studies of the interactions of 5-FU, LV, MTX, and IFN.

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