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Short communication

Alpha-interferon in combination with 5-fluorouracil and leucovorin in metastatic colorectal cancer: a phase I study

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Summary. A high rate of response to 5-fluorouracil (5FU) and alpha-interferon (αIFN) combination therapy has been reported in metastatic colorectal cancer patients. Therefore, designed a trial of high-dose continuous-infusion 5FU, oral leucovorin (LV), and αIFN in this group of patients. Because this combination has not previously been tested and severe toxicity has been reported for 5FU and αIFN combination therapy, we conducted a phase I trial in which 11 patients presenting with previously untreated metastatic colorectal cancer were treated with escalating doses of αIFN together with fixed doses of 5FU and LV. WHO grade III toxicity consisting mainly of oral mucositis was noted in four patients. No grade IV toxicity occurred. Although αIFN may enhance the toxicity of 5FU, the toxicity of this regimen remained manageable. Three partial responses were noted.

Introduction

Single-agent therapy with 5-fluorouracil (5FU) in patients exhibiting colorectal cancer produces a response rate of approximately 20%, with no significant impact on survival being noted [11]. Leucovorin (LV) displays a synergistic effect with 5FU by inhibiting the enzyme thymidylate synthetase (TS), resulting in increased suppression of DNA synthesis by 5FU [7, 10]. Randomized clinical trials using different schedules of administration of 5FU and LV versus 5FU monotherapy have been reported [3, 6, 13, 15–18], and although several of these studies demonstrated a modest increase in the response rate, survival was not always improved.

The use of alpha-interferon (αIFN) in combination with 5FU has recently produced a 63% partial response rate in 32 previously untreated colorectal cancer patients [19]. Several grade III and IV (WHO) toxicities were recorded, including 3 toxic deaths. This study has been repeated by two other groups [9, 14], who recorded substantial toxicity that necessitated dose reductions in the majority of cases; the response rates achieved in these studies were only 26% and 35%, respectively.

The rationale for the combination of 5FU and αIFN is based on the observation that these agents exert synergistic cytotoxic effects in vitro [4, 21]. Proposed pathways by which IFN may influence the action of 5FU include an increase in the formation of 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), resulting in the inhibition of TS activity [5]; a decrease in the plasma clearance of 5FU [8]; augmentation of the incorporation of 5FU into RNA [12]; and a decrease in the resistance to 5FU as a consequence of the abolition of increased expression of the gene encoding for TS [2].

The addition of LV to 5FU and αIFN is a reasonable step. The schedule of administration of high-dose continuous-infusion 5FU and oral LV used in the present study was based on the results of a recent pilot study in which the feasibility of this regimen was tested in 31 patients presenting with advanced colorectal cancer [1]. The treatment was well tolerated, with grade III/IV (WHO) toxicity occurring in only 8 patients: 1 subject experienced grade IV diarrhea, and 7 developed grade III diarrhea or vomiting. The present report describes the results we obtained using escalating doses of αIFN in combination with this regimen of 5FU and LV in patients exhibiting metastatic colorectal cancer.

Patients and methods

Patients. Eligibility criteria included histologically proven metastatic colorectal adenocarcinoma that was not amenable to surgical resection, bidimensionally measurable disease, a WHO performance status of ≤ 2, an age of between 18 and 75 years, no prior chemotherapy, no radiotherapy on indicator lesions, no CNS involvement, serum creatinine values of ≤ 150 μmol/l, serum bilirubin levels of ≤ 25 μmol/l, a WBC of $\geq 4 \times 10^9$/l, and a platelet count of $\geq 100 \times 10^9$/l. Informed consent

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Table 1. Toxicity observed in 11 patients receiving 5FU, αIFN, and LV as combination therapy for metastatic colorectal cancer

αIFN (MIU/dose)	3	5	8		10	
Patients (*n*)	3	6	8		5	
Grade of toxicity	I/II	I/II	I/II	III	I/II	III
Fever	1	3	5	0	3	1
Flu-like symptoms	0	3	7	0	3	0
Fatigue	1	4	5	1	4	1
Mood alterations	0	1	1	0	3	0
Anorexia	2	4	3	1	2	0
Decline in performance	0	1	1	1	2	0
Nausea/vomiting	1	1	3	0	1	1
Diarrhea	0	1	4	0	3	1
Mucositis	0	2	3	1	3	2
Leukopenia	0	0	1	1	0	0
Renal dysfunction	0	0	1	0	0	0

Data represent numbers of patients. The maximal toxicity observed in each patient during the study is presented

was obtained from all patients. In all, 11 subjects were enrolled in the study. Their median age was 61 years (range, 37–73 years) and their median WHO performance status, 1 (range, 0–2). The primary tumor of 7 patients was located in the colon and that of the other 4, in the rectum. The predominant site of metastatic disease was the liver (8 cases).

Study design. Each treatment cycle consisted of a continuous i.v. infusion of 60 mg/kg 5FU over 48 h on days 1 and 2 given by a portable infusion device (Deltec, Pharmacia) through an s.c.-implanted venous catheter (Port-A-Cath, Pharmacia), together with 90 mg LV given orally every 6 h (×8) starting at 1 h prior to 5-FU administration. αIFN was given s.c. on days 1, 3, and 5. Cycles were given weekly for 4 consecutive weeks and then every 2 weeks thereafter. If toxicity permitted, the αIFN dose was escalated once in every patient after 2 weeks of treatment. In first three patients, it was escalated from 3 to 5 MIU/dose; in the next three, from 5 to 8 MIU/dose; and in the last five, from 8 to 10 MIU/dose. No further escalation was planned. αIFN (rIFNα-2b, Intron A) was supplied by Schering (Essex, UK).

The first treatment cycle was given on the oncology ward; thereafter, treatment was continued on an outpatient basis. Patients were evaluated for toxicity after each cycle and for response after six cycles. When toxicity of grade ≥III occurred, treatment was withheld until values had returned to the normal range and/or symptoms had disappeared. A 50% reduction in the dose of 5FU was allowed for diarrhea, mucositis, and myelosuppression of grade ≥III, and a 50% reduction in the αIFN dose was allowed for constitutional symptoms of grade ≥III. In the case of other toxicities, dose reduction was left to the discretion of the investigator. WHO guidelines for toxicity and response were used. Non-WHO toxic symptoms were scored as follows: 0, none; 1, mild; 2, moderate; 3, severe; and 4, life-threatening.

Results

Toxicity

A median of 14 cycles (range, 4–28) were given to 11 patients. The toxicity of this regimen is summarized in Table 1 as the worst toxicity recorded; in all cases, these side effects occurred during the first 4 weekly cycles. Fever and flu-like symptoms generally responded well to between one and three doses of 500 mg oral acetaminophen.

Grade IV toxicity was not observed in any patient during the study. No grade III toxicity was recorded at αIFN doses of 3 and 5 MIU. Four subjects experienced grade III toxicity at doses of 8 and 10 MIU αIFN, with oral mucositis being most prominent. In three of these patients a reduction in the dose of 5FU was undertaken; in one case the αIFN dose was also lowered due to fatigue. Treatment was well tolerated following dose reductions. All grade III toxicity at 8 MIU αIFN occurred in the fourth patient, who was removed from the study. Although this man completely recovered from several concurrent grade I–III toxicities, the continuation of treatment was not considered to be in his best interest. This patient was known to exhibit Crohn's disease as well as short bowel as a consequence of previous surgery. He received no additional treatment other than dietary advice at the start of chemotherapy.

After the fourth cycle, at which point chemotherapy was given every 2 weeks, treatment was tolerated better and no dose reductions were necessary.

Response

Although the evaluation of toxicity was the primary goal of this study, ten patients were also evaluated for response. Three subjects (30%) achieved a partial response after completing six cycles, the duration of response being 3, 6, and 9 months, respectively. Responses occurred at αIFN doses of 5 and 8 MIU. Two other patients who had been treated with αIFN at doses of 8 and 10 MIU, respectively, continued to exhibit stable disease parameters after the completion of treatment (28 cycles). The remaining five patients displayed progressive disease after receiving a median of 12 (range, 7–24) cycles.

Discussion

We conducted a trial of high-dose continuous-infusion 5FU, LV, and αIFN in colorectal cancer patients. The feasibility of the 5FU/LV schedule had been demonstrated in a prior study [1]. Regarding the possible mechanisms of action of αIFN plus 5-FU [2, 5, 8, 12] it is likely that αIFN increases the toxicity of 5FU. Therefore, a phase I trial was initiated in which patients received a fixed dose of 5FU and LV along with αIFN doses escalating from 3 to 10 MIU/dose. Further escalation of the αIFN dose was not planned because the high response rate previously reported for αIFN and 5FU was achieved using a comparable αIFN dosing schedule [19]. Moreover, the results of a recent phase I trial of αIFN and 5FU suggest that higher doses of αIFN may even negatively influence the response rate [20].

We did not record any grade IV toxicity, and grade III toxicity occurred only at the two highest doses of αIFN. The 5FU dose was reduced in three patients, mainly because of grade III oral mucositis, and in one of these cases the αIFN dose was also lowered. Treatment was discontinued in one patient due to numerous concurrent grade I–III toxicities. All other side effects were easily manageable without dose reduction.

We conclude that outpatient treatment consisting of αIFN injected at 10 MIU/s.c. dose three times weekly

together with 5FU delivered by continuous i. v. infusion at 60 mg/kg over 48 h and LV given orally at 720 mg in eight doses may be safely carried out. The toxicity observed during the present study compares favorably with that reported for other trials in which 5FU and αIFN combination therapy was given [9, 14, 19]. We are currently performing a phase II trial in colorectal cancer patients using this treatment schedule.

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