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Clinical paper

Pharmacokinetics of recombinant human interferon-α2a combined with 5-fluorouracil in patients with advanced colorectal carcinoma

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We evaluated the pharmacokinetics of 5-fluorouracil (5-FU) combined with recombinant human interferon (IFN)-α2a in 10 previously untreated patients with advanced colorectal carcinoma. 5-FU was administered as a continuous i.v. infusion, 750 mg/m^2/day for 5 days during week 1. One s.c. injection of IFN-α2a, 9×10^6 IU, was administered during week 2. Beginning with week 3, a continuous i.v. infusion of 5-FU 750 mg/m^2/day for 5 days was administered in combination with IFN-α2a, 9×10^6 IU s.c. three times per week. The combination of 5-FU and IFN-α2a was continued every other week until either 3 months after complete remission or tumor progression. No grade 4 toxicity was observed. Granulocytopenia (two patients), leukopenia (one patient), thrombocytopenia (one patient), stomatitis (two patients), fatigue (one patient) and hand–foot syndrome (one patient) were the major (grade 3) toxic reactions encountered. Overall, one complete and six partial responses were noted. The results of the paired *t*-test showed no statistically significant differences between the means of the two treatments, 5-FU and 5-FU plus IFN-α2a, with respect to the steady-state plasma concentration, area under the concentration–time curve, total body clearance, or steady-state volume of distribution of 5-FU, or the serum concentration of IFN. We conclude that 5-FU and IFN-α2a do not interact pharmacokinetically at the doses and schedules in the regimen studied. [© 1998 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, colon carcinoma, colorectal carcinoma, interferon, recombinant human interferon-α2a.

Introduction

5-Fluorouracil (5-FU) remains the most active single agent in the treatment of advanced colorectal carcinoma. As a single agent, 5-FU has shown a response rate of approximately 15–20% without any significant impact on overall survival. Despite the development of new drugs, no new agent has proven to be more active than 5-FU against advanced colorectal carcinoma.[1–3] Therefore, there is continued impetus to investigate the biomodulation of 5-FU. Several clinical trials have demonstrated an increased response rate of 5-FU in combination with leucovorin,[4,5] but there is no conclusive evidence of increased response when other biomodulatory agents, i.e. *N*-(phosphonoacetyl)-L-aspartate, cisplatin, hydroxyurea, thymidine, methotrexate and interferon (IFN)-α, are combined with 5-FU.

A series of phase II trials of 5-FU combined with IFN-α[6–9] was conducted after a pilot study by Wadler *et al.*[10] demonstrated a response rate of 76% [95% confidence interval (CI): 56–96%] in patients with previously untreated colorectal carcinoma. In a follow-up study, a 42% response rate was ultimately reached.[11] The regimen developed by Wadler *et al.*[10] used an initial 120 h i.v. infusion of 5-FU during the first week of therapy followed by a weekly bolus and s.c. injection of IFN-α2a, 9×10^6 IU three times per week. Other phase II trials, however, using the same regimen failed to confirm the high initial response rate that Wadler *et al.* achieved; they demonstrated response rates between 24 and 35%.[6–9] Previously reported pharmacokinetic studies demonstrated variable effects of IFN-α on the pharmacokinetics of 5-FU.[12–18]

We therefore decided to evaluate the pharmacokinetic profile of 5-FU and IFN-α2a alone and in combination. Our schedule differed from that of Wadler *et al.* in that in our study 5-FU was always administered as a continuous i.v. infusion when given in combination with IFN-α2a. The baseline pharmacokinetic profiles of 5-FU and IFN-α2a were obtained during weeks 1 and 2, respectively. During week 3, the pharmacokinetic profile of 5-FU and IFN-α2a

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administered in combination was then determined. Information regarding toxicity, the objective response rates, and time to and duration of response were also collected and are reported herein.

Patients and methods

Patient eligibility

Ten patients who were at least 18 years of age, who had histologically proven metastatic, recurrent or surgically unresectable colorectal carcinoma, and who had received no prior chemotherapy were entered into this trial. Patients with prior radiotherapy were allowed, provided the indicator lesions were outside the radiation field and at least 30 days had elapsed since completion of radiation. Patients were excluded from the trial if they had intercurrent infection, impaired renal function (serum creatinine >2.0 mg/dl), impaired hepatic function (bilirubin >2.0 mg/dl, prothrombin time >3 s above control or serum albumin <2.0 mg/dl), prior use of IFN-α, impaired hematologic function (granulocytes $<1500/mm^3$, platelets $<100\,000/mm^3$, hemoglobin <10 g/dl or hematocrit $<30\%$), a history of seizure disorder or metastases in the central nervous system. Written informed consent was obtained before enrollment in the trial. This trial was conducted according to the principles of the Declaration of Helsinki. The protocol and consent form were approved by the Institutional Review Board.

Study design

This was an open trial of 5-FU and IFN-α2a at a single study center. Starting with week 1, 5-FU at 750 mg/m^2/day by a continuous i.v. infusion was administered for 5 days, during which time the 5-FU pharmacokinetic data were collected. During week 2, a single s.c. dose of IFN-α2a at 9×10^6 IU was administered, after which the IFN-α2a pharmacokinetic data were obtained. During week 3, the patients received the combination of 5-FU at 750 mg/m^2/day as a continuous i.v. infusion on days 1–5 and IFN-α2a (Roferon; Hoffmann-La Roche, Nutley, NJ) at 9×10^6 IU s.c. on days 1, 3 and 5. The pharmacokinetic data for both 5-FU and IFN-α2a were obtained during week 3. After a 1 week rest period, the patients received the combination of 5-FU and IFN-α2a every other week until either 3 months after complete remission or tumor progression. The rate of the continuous i.v. infusions of 5-FU was controlled by an i.v. infusion pump device on an inpatient (IMED model 980; IMED, San Diego, CA) and outpatient (INFUMED model 30; Medinfusion, Atlanta, GA) basis. IFN-α2a (9×10^6 IU/2 ml IFN-α2a, recombinant; Hoffmann-La Roche) was supplied as a 9×10^6 IU per vial solution. 5-FU (500 mg/10 ml) was supplied by Hoffmann-La Roche as a solution in 10 ml single-use vials. Dose reductions of 5-FU were allowed for stomatitis, diarrhea and hematologic toxicity. IFN-α2a doses were adjusted for renal, hepatic and neurologic toxicity. For toxicity of grade ≥2, treatment was discontinued until the patient recovered. Then the subsequent dose was reduced by 25%.

Blood sample collection

Seven milliliters of blood was collected into vacutainer tubes before the study began as a baseline measurement for control purposes. Thereafter, 7 ml of blood was collected at multiple points to determine the pharmacokinetic profiles of 5-FU alone during week 1, of IFN-α2a alone during week 2 and of combination therapy during week 3. Blood samples for the pharmacokinetic analysis of 5-FU were collected at 0 (predose), 3, 6, 24, 48, 72, 96 and 119 h after the start of the 5-FU infusion during both week 1 and week 3. Blood samples for the pharmacokinetic analysis of IFN-α2a were collected at 0 (predose), 3 and 6 h after IFN-α2a administration during week 2 and week 3.

Analytical methods

Serum concentrations of IFN were determined by a specific enzyme immunoassay procedure based on the sandwich technique. IFN was captured and labeled simultaneously by incubating the samples and IFN standards in a single step with mouse anti-IFN monoclonal antibody-coated beads[19] and mouse anti-IFN monoclonal antibody peroxidase conjugate. The beads were then washed and incubated with enzyme substrate. The color development was proportional to the amount of bound enzyme. After the enzyme reaction was stopped, the absorbance was read at 492 nm. The readings were a direct measure of IFN concentration. Sample values were determined on a standard curve obtained from plotting absorbance versus IFN concentration.

Serum concentrations of 5-FU were determined by a specific gas chromatography–negative ion chemical ionization mass spectrometry procedure.[20] The assay uses an extraction method with ether–isopropanol followed by removal of the solvent by flash evaporation. The residue was dissolved in ethyl acetate and

evaporated to dryness under a stream of nitrogen. The remaining residue was dissolved in acetonitrile followed by the addition of ditrifluoromethylbenzyl bromide and triethylamine. After the solution was allowed to stand at room temperature, a precipitate was formed by adding ethyl acetate followed by hexane. The solution was passed through a Sephadex LH20 column, which was washed with an additional 1 ml of hexane. The eluent was concentrated to 0.5 ml and an aliquot was injected into the gas chromatograph/mass spectrometer.

The assay of 5-FU and IFN in the serum showed overall interassay precisions of 2.1 and 5.2%, respectively, and intra-assay precisions of 7.6 and 9.1%, respectively. The lower limit of quantitation was 10 IU/ml for IFN and 1 ng/ml for 5-FU using 0.1 and 0.25 ml of serum, respectively.

Pharmacokinetic evaluation

Pharmacokinetic parameters for 5-FU were obtained from individual serum concentration–time data using a two-compartment i.v. infusion pharmacokinetic model with the aid of a PCNONLIN (SCI Software, Lexington, KY) computer program for a non-linear least-squares regression analysis. Differences in the pharmacokinetic parameters of 5-FU or the serum concentrations of IFN between the two treatments, 5-FU and 5-FU plus IFN-α2a, were assessed by paired *t*-test analysis. A difference was considered significant if the probability of chance explaining the results was less than 5% ($p < 0.05$).

Results

All 10 patients were evaluated for the pharmacokinetics of 5-FU and IFN-α2a. Table 1 summarizes the demographic data and baseline characteristics of the study population.

Mean profiles of the serum concentrations for 5-FU are shown in Figure 1. A two-compartment i.v. infusion pharmacokinetic model was used to fit the 5-FU serum concentration–time profile (both during and after infusion) for each patient and each treatment. The reliable pharmacokinetic parameters were the steady state serum concentration (C_{ss}) and initial decreasing (distribution phase) half-life after termination of the infusion. Mean pharmacokinetic parameters generated from PCNONLIN with the results of the statistical analysis are summarized in Table 2. The mean serum concentrations of IFN are plotted against time in Figure 2 and are statistically

Table 1. Summary of patient demographic data

Variable	Value
Sex	
male	7
female	3
Age at treatment (years)	
mean ± SD	51 ± 14
range	28–74
Weight at screening (kg)	
mean ± SD	79.9 ± 23.4
range	44.9–130.2
Height (cm)	
mean ± SD	174 ± 11
range	155–193
body surface area (m^2)	
mean ± SD	1.99 ± 0.35
range	1.41–2.68
Race	
White	9
Hispanic	1

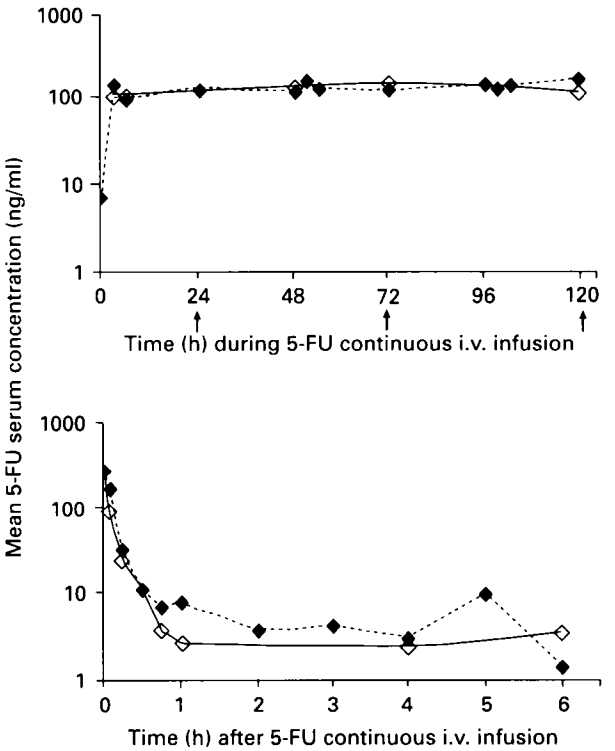

Figure 1. Mean 5-FU serum concentration–time profiles (ng/ml) during and after 750 mg/m^2/day continuous i.v. infusion for 5 days. [Week 1 (◇) represents administration of 5-FU alone; week 3 (◆) represents combination therapy with IFN-α2a at 9×10^6 IU s.c. on days 1, 3 and 5 of the 5-FU infusion; ↑ represents IFN-α2a dose during week 3.]

Table 2. Summary and statistical analysis of mean 5-FU pharmacokinetic parameters

Variable	N	Week 1	Week 3	Difference (SE)	p value[a]
V_d (l)	9	428.2	276.2	−152.0 (65.8)	0.05
AUC (mg·min/ml)	9	1136	1133	−3 (103)	0.98
α (min $^{-1}$)	7	0.1048	0.2288	0.1240 (0.0951)	0.24
β (min $^{-1}$)	10	0.0041	0.0004	−0.0037 (0.0023)	0.15
C_{SS} (ng/ml)	9	149.4	150.6	1.2 (16.4)	0.95
Clearance (l/min)	9	10.71	12.72	2.01 (1.65)	0.26
V_{SS} (l)	9	66750	13287	−53463 (42648)	0.25

SE, standard error of mean difference.
Week 1=5-FU alone therapy.
Week 3=5-FU plus IFN-α2a combination therapy.
[a]Statistical significance (two-sided test) of the paired t-test.

summarized in Table 3. Interpatient variability was high (coefficient of variation > 50%) for both the serum concentrations (5-FU and IFN) and the pharmacokinetic parameters (5-FU). No statistically significant differences were found between the means of the two treatments with respect to the area under the concentration-time curve (AUC), distribution phase rate constant (α), terminal elimination rate constant (β), C_{ss}, total body clearance or steady-state volume of distribution (V_{ss}) of 5-FU (Table 2) or with respect to serum concentrations of IFN (Table 3). A statistically significant difference was found between the mean of the 5-FU alone therapy and that of the 5-FU plus IFN-α2a combination therapy with respect to the volume of distribution (V_d); however, the significance of this parameter was trivial because there was no statistically significant difference in V_{ss}.

All patients were assessable for response and toxicity. Objective responses were observed in seven patients (one complete and six partial responses). One patient was considered to have achieved a complete response after an adjunctive surgical resection of a solitary 1.0 × 1.0 cm lesion in the right lobe of the liver. The median time to respond was 9.5 weeks (range 7–22 weeks). The median duration of response was 24 weeks (range 8–318+ weeks).

Toxicity is listed in Table 4. No grade 4 toxicity was observed. Overall, grade 3 toxicity was limited to granulocytopenia in two patients, leukopenia in one patient, thrombocytopenia in one patient, stomatitis in two patients, fatigue in one patient and hand-foot syndrome in one patient.

Discussion

The schedule chosen for the combination of 5-FU and IFN-α2a in this pharmacokinetic study differs from the regimen developed by Wadler *et al.*,[10] in which s.c. IFN-α2a was administered at 9×10^6 IU three times

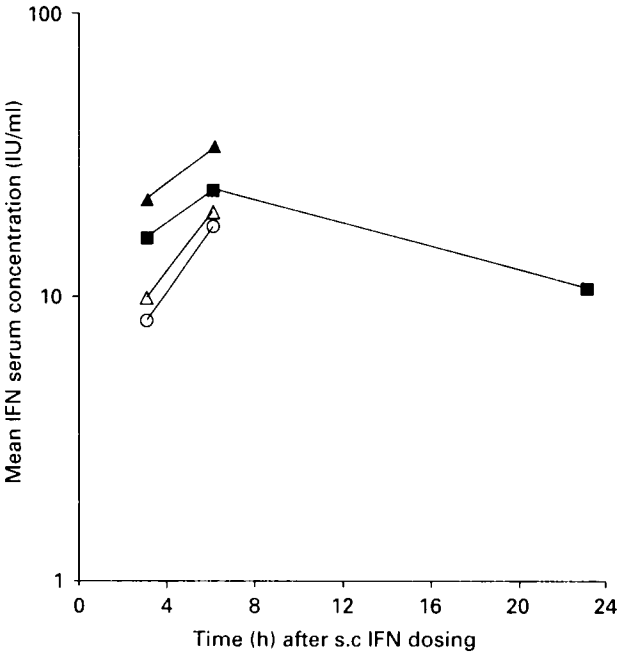

Figure 2. Mean IFN serum concentration–time profiles following a single s.c. dose of 9×10^6 IU IFN-α2a (week 2) or concomitant administration with 5-FU (week 3): △, week 2; ○, week 3, first dose; ▲, week 3, second dose; ■, week 3, third dose.

Table 3. Summary and statistical analysis of IFN serum concentrations after a single injection during week 2 and the first injection during week 3

Time after dosing (h)	N	Mean IFN concentration (IU/ml)			p value[a]
		Week 2	Week 3	Difference (SE)	
3	6	14.817	13.818	−0.999 (1.8355)	0.61
6	9	22.480	19.824	−2.656 (1.6938)	0.16

SE, standard error of mean difference.
Week 2=IFN-α2a alone therapy.
Week 3=5-FU plus IFN-α2a combination therapy (first dose).
[a]Statistical significant (two-sided test) of the paired t-test.

weekly and 5-FU was administered concomitantly as a continuous i.v. infusion at 750 mg/m^2/day for 5 days. Following a 7 day hiatus, subsequent 5-FU doses were administered weekly as an i.v. bolus at 750 mg/m^2. The regimen of Wadler *et al.* was modified for this clinical trial in response to a pilot study by Pazdur *et al.*[21,22] Thus, in this study during week 1, 5-FU was administered as a continuous i.v. infusion for 5 days without concomitant IFN-α2a. Withholding IFN-α2a allowed collection of baseline pharmacokinetic parameters for 5-FU alone. A single injection of IFN-α2a was administered during week 2 so that baseline serum levels for this agent could be obtained. Beginning with week 3, the combination was administered for the first time and, unlike Wadler *et al.*'s schedule, the 5-FU was always administered as a 120 h continuous i.v. infusion at 750 mg/m^2/day together with s.c. IFN-α2a three times a week at 9×10^6 IU. During the third week of the clinical trial, serum samples for pharmacokinetic parameters of both drugs were collected.

Table 4. Overall toxicity

Toxicity	Grade			
	1	2	3	4
Granulocytopenia	1	2	2	0
Leukopenia	6	4	1	0
Thrombocytopenia	2	1	1	0
Nausea	8	2	0	0
Vomiting	2	1	0	0
Stomatitis	9	4	2	0
Diarrhea	3	6	0	0
Fatigue	9	2	1	0
Headache	3	1	0	0
Fever	6	7	0	0
Skin reaction	3	5	0	0
Hand–foot syndrome	7	4	1	0

Several phase I safety and pharmacokinetic studies (Table 5) have demonstrated a decrease in 5-FU clearance and an increase in 5-FU AUC when this drug is administered concurrently with IFN-α.[12–14,17,18] However, in other studies, changes in 5-FU pharmacokinetics were not demonstrated when IFN-α was added.[15,16] These differences may be explained by variations in the dose, schedule or sequence in which the drugs were administered.

The pharmacokinetic parameters of 5-FU observed in our study after the 5 day continuous i.v. infusion at 750 mg/m^2/day are consistent with the pharmaco-

Table 5. Overview of pharmacokinetic studies of 5-FU and IFN-α

Reference	Dose and schedule	Effect on 5-FU
Lindley et al.[12]	5-FU, 300 mg/m^2 i.v. CI starting day 1 IFN (2, 3.5, 5 or 10) $\times 10^6$ IU/m^2 starting day 2	plasma level increased
Grem et al.[13]	5-FU 370 or 425 mg/m^2 i.v. bolus (days 2–6) LV, 500 mg/m^2 (days 2–6) IFN (5 or 10) $\times 10^6$ IU/m^2 (days 1–7) or 3×10^6 IU/m^2 (days 1–14)	AUC increased; clearance decreased
Czejka et al.[14]	5-FU, 750 mg/m^2 i.v. bolus LV, 200 mg/m^2 ±IFN, (5 or 9) $\times 10^6$ IU	AUC increased
Patel et al.[15]	5-FU, 400 mg/m^2 i.v. bolus, then 400 mg/m^2 i.v. over 22 h LV, 200 mg/m^2 (2 h before 5-FU) IFN, 6×10^6 IU every 2 days	no effect
Sparano et al.[16]	5-FU (150, 200, 250 or 300)/m^2/day PCI IFN, 5×10^6 IU/m^2 3 ×/week 48 h after start of 5-FU	no effect
Danhauser et al.[17]	5-FU, 750 mg/m^2 i.v. CI × 5 days IFN (0.1, 0.25, 0.26, 1.0, 3.0, 5.0, 10.0 or 15.0) $\times 10^6$ IU every 14–21 days	clearance decreased
Schuller and Czejka[18]	5-FU, 750 mg/m^2 i.v. bolus every every week IFN, 5×10^6 IU 3× week ±LV, 200 mg/m^2 (immediately before IFN)	AUC increased; clearance decreased
Kim et al.	5-FU, 750 mg/m^2 i.v. CI × 5 days IFN, 9×10^6 IU × 1 (week 2) 5-FU, 750 mg/m^2 i.v. CI × 5 days IFN, 9×10^6 IU days 1, 3, 5 (week 3)	no effect

i.v. CI, intravenous continuous infusion; LV, leucovorin; PCI, protracted continuous infusion. See text for other abbreviations.

kinetic characteristics of 5-FU generated after a single i.v. dose (e.g. half-life = 11 min and ~20 h seen at very low concentrations). Comparison of the pharmacokinetic variables between week 1 (5-FU alone) and week 3 (5-FU combined with IFN-α2a) showed no statistically significant differences in any of the variables of 5-FU except for V_d; however, the difference between the means of the two treatments with respect to V_d was of minimal clinical significance because V_{ss}, a more meaningful and relevant variable, was not significantly different. Corresponding mean serum concentrations after s.c. injection of IFN-α2a during week 2 and on days 1, 3 and 5 of week 3 were comparable, suggesting that the 5-FU infusion did not alter the serum concentration of IFN.

Our study differed from those previously reported[12-14,17,18] in several aspects. Czejka *et al.*[14] and Schuller and Czejka[18] collected blood samples for only 60 min after an i.v. bolus dose of 5-FU. The elimination half-life reported ranged from 16 to 20 min in both studies, an indication of mixed α and β phases. Because the β phase may vary under a number of conditions (e.g. circadian changes), contamination of the α phase values may lead to errors. The results of Czejka *et al.*,[14] Grem *et al.*,[13] and Schuller and Czejka[18] were based on a calculated AUC (initial plasma concentration at time 0 divided by the elimination rate constant) rather than a measured AUC (by the trapezoidal rule).

The change in the calculated AUC of 5-FU after IFN-α2a injections appeared to be marginal. Czejka *et al.*[14] failed to observe a significant difference in the β and V_d (the product of the two is clearance), and yet they did observe a significant difference in clearance and AUC.

In addition, the change in AUC for 5-FU after IFN-α2a injections was found to be very small (~1.3-fold)[13] and not supported by a change in clearance (at one IFN-α2a dose, clearance changed with a change in V_d, and at another IFN-α2a dose, clearance did not change).

The results of Danhauser *et al.*[17] showed that treatment with IFN-α2b concurrent with 5-FU infusion increased 5-FU C_{ss} by 28% and decreased 5-FU clearance by 20–35%. Although the observation was documented, the interpretation that the change was due to a pharmacokinetic interaction of 5-FU with IFN-α2b was incorrect. This discrepancy can be attributed to the authors' assumption that a 100% steady state would have been reached 16–21 h after the start of the infusion of 5-FU.

Our data (Figure 1) clearly demonstrated that the 5-FU C_{ss} gradually reached ~100% 3 days after the start of 5-FU infusion. By measuring 5-FU at 48 and 72 h (which was similar to the design used by Danhauser *et al.*[17]), one would artifactually conclude that IFN-α2a caused a mean increase in C_{ss} of 16% at 48 h and 36% at 72 h. The clearance was a secondary parameter because it was derived from the relationship: clearance = infusion rate/C_{ss}. Consequently, the resulting clearance was similar to that of C_{ss}. Our analysis was also consistent with the authors' finding that there was no relationship between the IFN-α2a dose and 5-FU C_{ss} elevation.

Clinical trials by Patel *et al.*[15] and Sparano *et al.*,[16] using a different dose and schedule of 5-FU and IFN-α2a, indicated similar negative results as we observed in our study. Patel *et al.*[15] demonstrated the elimination half-life of 5-FU to be approximately 10 min, which was consistent with our values. Although evidence suggests that there may be a circadian pattern of 5-FU plasma levels,[23] Sparano *et al.*[16] showed that this variation was not influenced by IFN-α2a. Thus, a literature review and our data analysis suggest only a marginal, if any, alteration in 5-FU pharmacokinetics in the presence of IFN-α administration. This negative to minor change in 5-FU pharmacokinetics may be due to the doses of 5-FU and IFN-α as well as their dosing schedules.

Several phase III trials comparing 5-FU and 5-FU in combination with IFN-α failed to show improved response or survival rates in patients with advanced colorectal cancer.[24-26] In fact, the addition of IFN-α2b to 5-FU increased toxicity.[27] In addition, two randomized clinical trials demonstrated similar response rates in patients treated with 5-FU and leucovorin and in those who received 5-FU and IFN-α.[27,28] Kosmidis *et al.*[27] even found decreased survival rates in patients treated with 5-FU and IFN-α2b. Similarly, the use of IFN-α combined with 5-FU failed to demonstrate superior activity in patients with advanced gastric or pancreatic carcinoma compared with single-agent 5-FU.[29,30]

Despite the initial enthusiasm over the combination of 5-FU and IFN-α, this treatment failed to demonstrate improved efficacy in the treatment of metastatic colorectal carcinoma compared with 5-FU alone or 5-FU modulated by leucovorin. A recently analyzed study of the adjuvant therapy of colon cancer conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP Trial C-05) also failed to show any improvement with the addition of IFN-α to 5-FU and leucovorin in the adjuvant treatment of patients with surgically resected Dukes' classification B and C colon carcinoma. The combination of 5-FU, leucovorin and IFN-α appears to be more toxic than 5-FU plus leucovorin, and has no advantage in disease-free or overall survival.[31]

The patients included in this trial were treated with a regimen similar to one that has previously been

reported in 39 patients with advanced colorectal cancer.[22] A response rate of 31% (95% CI: 17-48%) has been reported, with grade 3-4 toxicities being mucositis (nine patients), diarrhea (two patients), granulocytopenia (two patients) and fatigue (three patients). Comparable toxicity and activity of 5-FU combined with IFN-α2a are reported herein for the patients who were treated on this pharmacokinetic trial.

Conclusion

We conclude that no pharmacokinetic interactions exist between 5-FU and IFN-α at the doses and schedules studied in this regimen. As confirmed by a series of phase II and III trials, IFN-α does not increase the response rate of 5-FU alone or in combination with leucovorin in patients with advanced colorectal carcinoma. Also, IFN-α when combined with 5-FU and leucovorin in the adjuvant therapy of colorectal carcinoma does not appear to improve survival. Therefore, the addition of IFN-α to 5-FU or 5-FU regimens does not appear to enhance therapeutic activity.

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