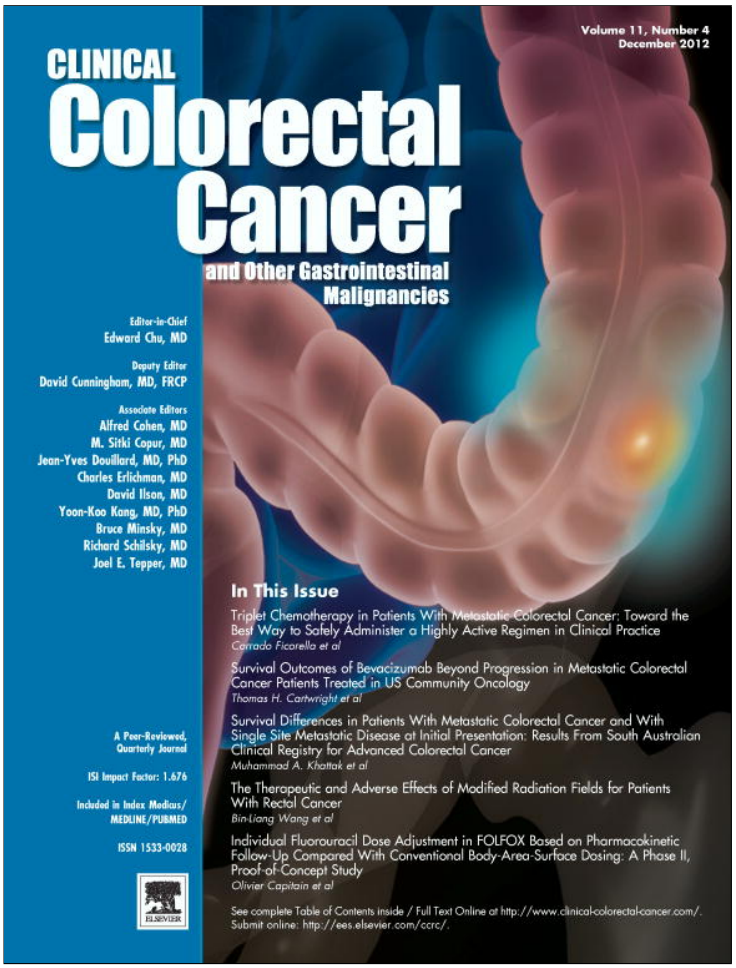

Original Study

Individual Fluorouracil Dose Adjustment in FOLFOX Based on Pharmacokinetic Follow-Up Compared With Conventional Body-Area-Surface Dosing: A Phase II, Proof-of-Concept Study

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Abstract

Patients with metastatic colorectal cancer were administered either individually determined pharmacokinetically adjusted 5-FU (fluorouracil) or 5-FU dosage by body surface area in FOLFOX (leucovorin, fluorouracil, oxaliplatin) chemotherapy. Efficacy and tolerability of an adjusted FOLFOX dosing was much higher than with body-surface-area dosing. Analysis of these results suggests that pharmacokinetically guided 5-FU therapy offers added value to combination therapy for metastatic colorectal cancer.

Background: To compare the efficacy and safety of pharmacokinetically (PK) guided fluorouracil (5-FU) dose adjustment vs. standard body-surface-area (BSA) dosing in a FOLFOX (folinic acid, fluorouracil, oxaliplatin) regimen in metastatic colorectal cancer (mCRC). **Patients And Methods:** A total of 118 patients with mCRC were administered individually determined PK-adjusted 5-FU in first-line FOLFOX chemotherapy. The comparison arm consisted of 39 patients, and these patients were also treated with FOLFOX with 5-FU by BSA. For the PK-adjusted arm 5-FU was monitored during infusion, and the dose for the next cycle was based on a dose-adjustment chart to achieve a therapeutic area under curve range (5-FU$^{\text{ODPM Protocol}}$). **Results:** The objective response rate was 69.7% in the PK-adjusted arm, and median overall survival and median progression-free survival were 28 and 16 months, respectively. In the traditional patients who received BSA dosage, objective response rate was 46%, and overall survival and progression-free survival were 22 and 10 months, respectively. Grade 3/4 toxicity was 1.7% for diarrhea, 0.8% for mucositis, and 18% for neutropenia in the dose-monitored group; they were 12%, 15%, and 25%, respectively, in the BSA group. **Conclusions:** Efficacy and tolerability of PK-adjusted FOLFOX dosing was much higher than traditional BSA dosing in agreement with previous reports for 5-FU monotherapy PK-adjusted dosing. Analysis of these results suggests that PK-guided 5-FU therapy offers added value to combination therapy for mCRC.

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Introduction

Colorectal cancer is one of the most frequent malignancies in humans. It represents a highly treatable and curable disease when localized, but, unfortunately, 50% of patients will experience metastatic progression associated with a poor prognosis. In an adjuvant or metastatic colorectal cancer (mCRC) settings, fluorouracil (5-FU) remains the cornerstone of treatment either as a single agent (10%-20% objective response rate [ORR])[1] or in combination therapy, such as FOLFOX (leucovorin, fluorouracil, oxaliplatin). In the past decade, objective response has been reported to increase to as much as 50% in 5-FU–based regimens associated with other cytotoxic agents, such as oxaliplatin and irinotecan,[2-5] and, more recently, with targeted therapies such as bevacizumab[6-8] or cetuximab.[9,10]

FOLFOX regimens have become the most commonly used treatment in first-line therapy for patients with mCRC.[11-13] Further

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modification of FOLFOX with newer agents has enabled a subgroup of patients with hepatic or pulmonary metastases to undergo secondary surgery with the resultant benefit of prolonged disease-free survival and for a few, a real hope of complete response (CR).[14-16] We previously demonstrated a beneficial relationship between systemic plasma levels of 5-FU and treatment efficacy and toxicity, and that both can be improved by means of pharmacokinetically (PK) dose adjustment.[17] An increased rate of objective response with a low incidence of toxic adverse effects was shown in a phase III randomized study of PK-guided treatment with 5-FU.[18]

Our goal in this study was to investigate the value of PK-guided 5-FU dose adjustment in improving efficacy and tolerance in the FOLFOX regimen in patients with mCRC. We performed our evaluation with a prospective study by assessing the prevention of oxaliplatin neurotoxicity with calcium-magnesium infusion by performing post hoc analysis on 2 groups of patients. Of the 157 patients, 118 patients were treated in 8 different institutions with 5-FU PK-guided therapy based on our previously published approach (5-FU$^{ODPM\ Tox}$ and 5-FU$^{ODPM\ Protocol}$, ODPM, Angers, France),[17] and 39 patients were treated in 2 other sister institutions and received 5-FU based on standard BSA dosing. The comparisons between the 2 groups were evaluated quantitatively, and no direct statistical comparisons were performed given that they were not randomized.

Patients and Methods

Patients

Patients from 10 hospitals with measurable pathologically confirmed metastatic adenocarcinoma of the colon or the rectum who were considered for first-line therapy with a FOLFOX regimen were eligible to participate in this study. To be eligible for inclusion, the patient had to be over 18 years, present with measurable metastatic lesions, and have an estimated life expectancy of at least 3 months. All patients were required to have normal bone marrow and organ function before the administration of drugs. The performance status was evaluated as defined by the World Health Organization. Written informed consent was obtained from all patients. Computed tomography (CT) was performed before treatment, and metastatic lesions were measured.

Treatment

FOLFOX was administered as follows: oxaliplatin was administered every 2 weeks, before 5-FU treatment, for 2 hours. The initial dose was 85 mg/m^2. Infusions of magnesium and calcium before and after oxaliplatin perfusion were administered to mitigate some of the known adverse effects of oxaliplatin therapy.[19] 5-FU was administered for 46 hours after treatment with 200 mg/m^2 of intravenous (I.V.) leucovorin bolus and 400 mg/m^2 of I.V. push 5-FU for 10 minutes.[11] The initial 5-FU dose was 2500 mg/m^2 and then was tailored according to our institute's practice, by using PK monitoring as previously described[18] according to 5-FU plasma concentrations during infusion (steady-state concentration) and dose-adjustment charts, adapted to a 46-hour duration of infusion with bolus injection and oxaliplatin association (5-FU$^{ODPM\ Tox}$ and 5-FU$^{ODPM\ Protocol}$).[17] Treatment was continued until progression was documented or severe toxicity took place, or according to the patient's or physician's decision.

Follow-Up

Every 2 weeks, each patient was physically examined and any adverse toxic events were evaluated and graded. Treatment efficacy was evaluated by comparing pretherapeutic metastatic lesion measurements to those remaining after 3 months of treatment and then every 3 months thereafter. Data were collected until the death of the patient or until the termination date of the study and any treatment administered after progression under the FOLFOX regimen was recorded.

Response Assessment

The response was assessed according to the Response Evaluation Criteria in Solid Tumor Group Criteria (RECIST 1.1 criteria) and by reviewing CTs. Measurable disease was defined as the presence of a lesion that could be bidimensionally measured by CT or by echography. Response to treatment was classified according to RECIST criteria. A panel of 2 independent radiologists reviewed the CTs of all patients. A CR required the disappearance of every lesion. A partial response (PR) required at least a 50% reduction in the cross-sectional area of all lesions. Stable disease required a lesion size decrease of $<$50%. Progressive disease categorization encompassed any situation in which any 1 lesion increased in cross-sectional size by more than 25% or a new lesion appeared. Duration of treatment and overall survival (OS) were characterized.

Safety Assessment

All adverse events, especially neuropathy and hematologic events were recorded and graded for severity according to National Cancer Institutes Common Terminology Criteria scale. Complete blood cell counts were performed every 2 weeks; electrolytes; kidney function, including urea and creatinine; and liver enzymes measurements were carried out every month. In the event of significant grade 2 toxicity for 5-FU, and without PK recommendations for a decrease, the dose was reduced by 10%. In cases of grade 3 toxicity or grade 2 for specific oxaliplatin neuropathy, the treatment was interrupted until toxic manifestations were resolved; treatment was then restarted with a decrease of 25% of 5-FU or oxaliplatin. Oxaliplatin was stopped if neuropathy grade 3 developed and 5-FU continued alone. Treatment was stopped in all cases of grade 4 toxicity.

Data Analysis

OS was defined by the period between the date of the start of treatment and the date of death, regardless of the cause. Progression-free survival (PFS) was defined by the period between the date of the start of treatment and the date of progression (clinical or radiologic progression) or death. All results of efficacy were considered in patients in intention to treat. Patients without progression at the time of analysis were censored at their last available follow-up assessment. The following baseline of well-known prognostic factors of survival, response, and toxicity (number of metastatic sites [1 vs. more]), performance status at enrollment of study (ECOG [Eastern Cooperative Oncology Group] 0 or 1 vs. 2), age ($<$60, 61-70, and $>$70 years), and sex were compared with each genotype by using the χ^2 test or Fisher test. Prognosis factors of efficacy and safety (especially oxaliplatin-induced neurotoxicity) were analyzed by logistic regression. The α error risk was classically chosen at 5%. Statistical analysis was performed on SAS 9.1.3 (SAS Institute INC, Cray, NC).

Table 1 Initial Characteristics of Patients and Tumors

Clinical Data	PK Monitored	BSA-Based Dose
Sex, n (%)		
Men	70 (59)	24 (62)
Women	48 (41)	15 (38)
Performance Status Grade, n (%)		
0-1	92 (78)	30 (77)
2-3	26 (22)	9 (23)
Median Age (Range), y	65.0 (35-81)	63.0 (32-80)
No. Metastatic Sites, n (%)		
1	81 (68)	28 (71)
2	30 (25)	9 (24)
3	7 (6.0)	2 (5.0)
Unique Metastatic Sites, n (%)		
Liver	66 (56)	23 (60)
Lung	11 (10)	4 (10)
Peritoneal Carcinomatosis or Nodes, n (%)	4 (5)	4 (4.9)

Abbreviations: BSA = body surface area; PK = pharmacokinetic.

Table 2 Distribution of Successive Lines of Therapy in the Whole PK Monitored Population of Patients (n = 118)

	2nd Line	3rd Line	4th Line	N (%)
No. Treated Patients and (Percentage According to Initial Population)	99 (83.9)	48 (40.7)	18 (15.3)	
Type of Chemotherapy				
FOLFIRI	58	3	0	61 (51.47)
FOLFOX	0	9	4	13 (11.0)
Targeted-Therapy Regimens	27	29	6	62 (52.5)
Intravenous 5-FU (FUFOL or LV5VU2 Regimen)	8	2	4	14 (11.9)
Oral 5-FU Prodrugs (Capecitabine)	6	5	4	15 (12.7)

Abbreviations: 5-FU = fluorouracil; FOLFIRI = leucovorin, fluorouracil, irinotecan; FOLFOX = leucovorin, fluorouracil, oxaliplatin; FUFOL = leucovorin, 5-fluorouracil (weekly 8-hour infusion); LV5VU2 = leucovorin, fluorouracil (biweekly 46-hour infusion).

Table 3 Distributions of Grade 3/4 Adverse Events

Adverse Event	% Dose-Monitored Regimen (n = 118)	% BSA-Based Dose Regimen (n = 39)
Diarrhea	1.7	12
Neutropenia	18	25
Mucositis	0.8	15
Thrombocytopenia	12	10

Abbreviation: BSA = body surface area.

Results

Patient Characteristics

A total of 118 patients who fulfilled the inclusion criteria were analyzed in the PK-adjusted group between November 2000 and January 2007. The median follow-up was 1426 days (3.9 years) with a range of 2.2-8.3 years. Clinical characteristics of the population of patients are given in Table 1. Thirty-nine patients were treated in 2 other institutions with the 5-FU dosage based on BSA. Their characteristics are also displayed in Table 1. The characteristics of all the patients were consistent with historical epidemiologic data in advanced colorectal cancer. In the monitored population of patients, the median age was 65 years (range, 35-81 years). 78% (92) of patients had good performance status of ECOG < 2. The male-to-female ratio was 1.45. At the time of enrollment in the study, 68.6% (81) of patients showed single metastases (82% (97) liver involvement). Tumor histologies were 100% adenocarcinoma. The successive treatments from second to fourth line, listed in Table 2, after failure of first-line therapy for patients in both groups, to evaluate the relevance for the analysis of OS. As expected, the number of treated patients decreased with number of subsequent lines as follows: 83.9% (99) second-line, 40.7% (48) third-line and 15.3% (18) fourth-line. About 51% (60) of the population received FOLFIRI (leucovorin, fluorouracil, irinotecan) regimen in second line; 52.5% (62) received one or several targeted therapies (especially cetuximab and/or bevacizumab). FOLFOX was reused in the third or fourth line when it was deemed appropriate (ie, after oxaliplatin-neuropathy resolution) in 11% of patients. Finally 24.6% of patients were also treated by 5-FU-only regimen either via I.V., or with oral analogues.

5-FU Dose Adjustment Due to PK Results. In the monitored group of patients as recommended by 5-FU$^{ODPM\ Tox}$ and 5-FU$^{ODPM\ Protocol}$, the mean (SD) 5-FU dosage at the first cycle was 94.32% ± 13.7% (theoretic dosage 2500 mg/m^2). The therapeutic dosage considered at 3 months of treatment was 110.47% ± 21.65% of the theoretic dosage (range, 60%-140%). Mean (SD) 5-FU plasma clearance was 130.59 ± 38.35 L.m^{-2}.h^{-1} (range, 59.82-245.73 L.m^{-2}.h^{-1}). At 3 months, the 5-FU dose was increased by at least 10% in 75 (63.55%) patients, with a mean (SD) increase of 20% ± 8% (range, 10%-40%). The increased dosage was higher than 20% in 42 (36%) patients, with a mean (SD) increase of 26% ± 6% (range, 20%-40%). However, the 5-FU dosage was decreased by at least 10% in 22 (18.64%) patients, with a mean (SD) decrease of 20% ± 9% (range, 10%-40%). The decrease dosage was higher than 20% in 14 (12%) patients, with a mean (SD) increase of 26% ± 5.94% (range, 20%-40%). In the group of patients in the BSA-based dosage group, the 5-FU dose was decreased in 4 patients 15% ± 4% (range, 10%-25%) within 3 months, because of grade 3 toxic adverse effects.

Safety. The safety results are shown in Table 3. In the dose-monitored group, grade 3/4 toxicity was 1.7% for diarrhea, 0.8% for mucositis, 18% for neutropenia, and 12% for thrombopenia; and the corresponding numbers were 12%, 15%, 25% and 10%, respectively, in the traditional BSA group.

Response to Therapy. In the PK-monitored arm, ORR was 69.7% at 3 months (2.5% CR plus 67.2% PR) and 55.7% at 6 months.

Table 4 Response Rates and Disease Control

Response Evaluation	Dose-Monitored Regimen, n (%)		BSA-Based Dose Regimen, n (%)
	At 3 mo	At 6 mo	At 3 mo
CR	3 (2.5)	23 (20.3)[b]	1 (2.6)
PR	80 (67.2)	40 (35.4)	17 (44)
OR = CR + PR	83 (69.7)	63 (55.7)	18 (46.6)
Disease Control	104 (88.1)	87 (77.0)	30 (77)
Disease Progression	14 (11.9)[a]	26 (23.0)	9 (23.0)

Abbreviations: BSA = body surface area; CR = complete response; OR = overall response; PR = partial response.
[a] At 6 months, 5 patients were dead.
[b] Surgery for metastases.

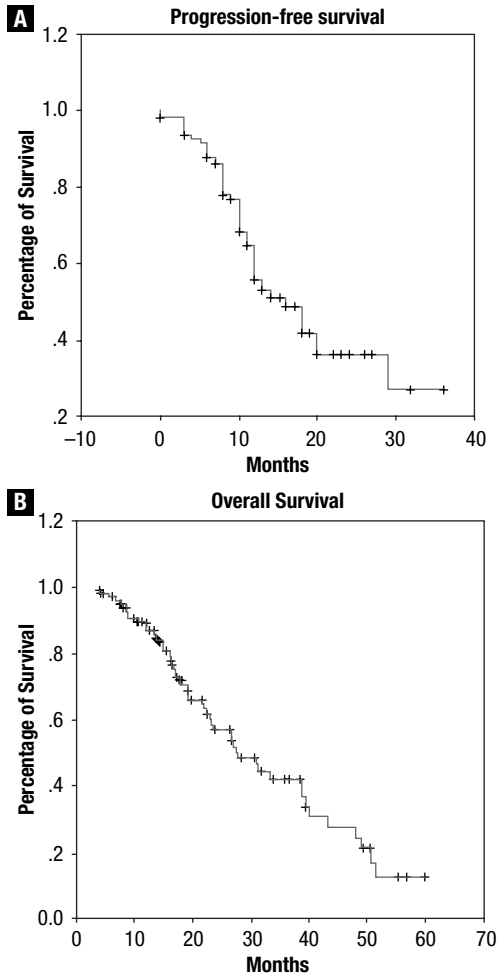
Median OS and median PFS in the PK-adjusted arm were 28 and 16 months, respectively (Table 4; Figure 1). PK-individualized FOLFOX showed a consistent efficacy, with 88.1% of disease control. Further analysis in this group revealed that secondary surgery of the metastases was carried out in 37 (31.3%) patients, with a median OS of 38.2 months vs. 16.6 months for nonoperative patients ($P <$ .0001).

In the patients with traditional BSA-dosage, ORR was 46% (2% CR and 44% PR), OS and PFS were 22 and 10 months, respectively (Table 4). The comparable disease control rate for BSA-dosed FOLFOX was 77%.

Discussion

PK-adjusted 5-FU monotherapy with folinic acid has been demonstrated to allow dose intensification and demonstrated to result in improved efficacy and favorable toxicity in patients treated for mCRC.[18,19] Because the standard of practice for the treatment of colorectal cancer has shifted toward combination therapy, the aim of the current proof-of-concept study was to further extend this type of approach in combination chemotherapy with FOLFOX. In this proof-of-concept study, we found an improvement in OS, PFS, and safety in the PK-dosed group compared with the BSA-dosed group. The proportion of patients who achieved ORR, OS, and PFS, and favorable reduction in grade 3/4 toxicity in the PK-dosing arm of this study were consistent with what was reported in earlier publications.[18,19] Even though the BSA-dosed group was not randomized with respect to 5-FU dosing in this study, the data used from these sites can be considered an appropriate comparison because the 2 institutions used the same standard treatment practice with the other 8 institutions where PK adjustment was used. Furthermore, we verified the validity of this group of comparators because the results we observed in the traditional BSA-dosed group of patients were consistent with previous studies as was the PK group.[3,11] It can thus be assumed that the group was a better comparator than historical controls. It is interesting to note that such tailored treatment enabled us to define a treatment schedule that proved superior when compared with previous studies with an acceptable toxicity profile for 5-FU, given that the actual 5-FU dose had to be more frequently increased than decreased. We can deduce that 36% of the patients were underdosed by at least 20%, with an average of 26% when considering the optimal target exposure. It is important to note that 5-FU plasma kinetics is not linear, in that an increase of 5-FU plasma levels is not simply proportional to the increase of the dose.[20]

Figure 1 Progression-Free Survival (A) and Overall Survival (B) of Patients Treated With a Tailored Fluorouracil Dose (n = 118)



Clinical Practice Points

- To date, very little data exist on therapeutic individualization of 5-fluorouracil using PK-monitored adjustment. In clinical practice today, 5-FU dosages are still calculated using body surface area (BSA) alone.
- Only one other study has shown the benefit of treatment adjustment with a 5-FU-based regimen.
- This retrospective study clearly demonstrates for the first time the superiority of PK-adjustment in FOLFOX protocols.
- Results in the PK-adjusted arm - objective response, median overall survival and median progression-free survival - were higher than in the BSA dosage group.

- At the same time, grade III and IV toxicities were lower in the PK-adjusted arm. This study provides further justification for PK-adjusted FOLFOX protocols coming into regular clinical use.

Conclusion

If our results of tailored FOLFOX therapy are confirmed in a randomized phase III study, either with FOLFOX alone or in combination with newer targeted therapies, the results would provide further justification for generalizing this approach in using an old and effective drug much more optimally when comparing the results of these data with adding newer agents in BSA-based FOLFOX. In line with this statement, and as an example, 2 randomized studies that recently compared first-line 5-FU plus folinic acid therapy to the same drugs plus irinotecan found no difference in terms of PFS and OS in second-line therapy.[21,22]

A caveat to the interpretation of our results is the post hoc retrospective design and the small number of patients, although the data for ORR and PFS were reasonably close to what would be expected from our prior observations. Thus, the implications of this study would indicate that PK-adjusted therapy with 5-FU by itself would likely result in lower cost and toxicity when compared with the added cost of newer therapies and when considering the modest added benefit of these newer therapies such as cetuximab,[23] or bevacizumab,[24] and as reviewed in a very recent publication.[25] Alternatively, 5-FU PK modulation combined with such targeted therapies could be an optimal approach in first-line treatment. In addition, this approach has the potential to enable a subgroup of patients with hepatic or pulmonary metastases to undergo secondary surgery with a potential for CR.

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Disclosure

The authors have stated that they have no conflicts of interest.

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