

Individual Fluorouracil Dose Adjustment Based on Pharmacokinetic Follow-Up Compared With Conventional Dosage: Results of a Multicenter Randomized Trial of Patients With Metastatic Colorectal Cancer

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ABSTRACT

Purpose

A phase III, multicenter, randomized study compared conventional dosing of fluorouracil (FU) plus folinic acid with pharmacokinetically guided FU dose adjustment in terms of response, tolerability, and survival.

Patients and Methods

Two hundred eight patients with measurable metastatic colorectal cancer were randomly assigned to one of two arms: arm A (104 patients; 96 assessable), in which the FU dose was calculated based on body-surface area; and arm B (104 patients; 90 assessable), in which the FU dose was individually determined using pharmacokinetically guided adjustments. The initial regimen was 1,500 mg/m² FU plus 200 mg/m² folinic acid infusion during a continuous 8-hour period administered once weekly. FU doses were adjusted weekly in arm B based on a single-point measurement of FU plasma concentrations at steady state until the therapeutic range (targeted area under the curve 20-25 mg·h·L⁻¹) previously established in other studies was reached.

Results

An intent-to-treat analysis of the 208 patients showed the objective response rate was 18.3% in arm A and 33.7% in arm B ($P = .004$). Median overall survival was 16 months in arm A and 22 months in arm B ($P = .08$). The mean FU dose throughout treatment was 1,500 mg/m²/wk in arm A and 1,790 ± 386 mg/m²/wk (range, 900 to 3,300 mg/m²/wk) in arm B. Toxic adverse effects were significantly more frequent and severe in arm A compared with arm B ($P = .003$).

Conclusion

Individual FU dose adjustment based on pharmacokinetic monitoring resulted in significantly improved objective response rate, a trend to higher survival rate, and fewer grade 3/4 toxicities. These results support the value of pharmacokinetically guided management of FU dose in the treatment of metastatic colorectal patients.

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INTRODUCTION

The use of drug combinations has transformed metastatic colorectal cancer treatment, with fluorouracil (FU) remaining the cornerstone of this treatment.¹⁻⁶ Although initial intensification of FU, in combination with other drugs, is the widely used approach from the inception, questions arise as to when these regimens should be introduced, whether initially or as soon as a tumor escape is suspected. Two recent multicenter, randomized clinical trials have compared one versus two drugs in first-line therapy, and showed no substantial difference in overall survival (OS) and treatment duration in the combined group, and more importantly, the combined group

showed a higher toxicity than the one-drug group.⁵⁻⁸ Continuous infusion of FU permits a significantly increased dose that is well tolerated and impacts treatment effectiveness.^{1,9-13} Thus, the use of the simple, well-tolerated, and inexpensive FU plus folinic acid regimen would be justified, provided that first an optimized schedule can be determined, and then modified in case of progressive disease.

A number of studies have reported substantial interindividual pharmacokinetic variability, mainly because of the variability of the activity of the key enzyme, dihydropyrimidine dehydrogenase (DPD), in pyrimidine metabolism.^{11,14} The activity of DPD may vary as a result of genetic polymorphisms and follows a Gaussian distribution.^{15,16} A relationship

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has been shown between DPD activity in lymphocytes and FU plasma clearance.¹⁷⁻¹⁹ An identical standard dose may result in a therapeutic response with acceptable toxicity in some patients, unacceptable and possibly life-threatening toxicity in other patients, and no response and no toxicity in another group of patients.^{12,20}

Some studies have shown a relationship between systemic plasma levels of FU and treatment toxicity and efficacy, and demonstrated that both can be improved by means of pharmacokinetic dose adjustment.^{12,21-23} Increased objective responses have been demonstrated when higher FU area under the curve (AUC) values are maintained.^{12,20-22} In two earlier prospective clinical trials using weekly 8-hour continuous infusion of FU, with FU concentration measured at steady-state, we showed a relationship between individual pharmacokinetic parameters, and both efficacy and toxicity of treatment.^{12,20} In these studies, we established an AUC₀₋₈ of 20 to 25 mg·h·L⁻¹ as the optimal level, with values greater than 25 mg·h·L⁻¹ causing excessive toxicity, consistent with results reported in other studies of colorectal and head and neck cancers.²¹⁻²⁵

Our goal in this study was to demonstrate the value of pharmacokinetically guided, FU dose adjustment in controlling toxicity, and improving efficacy and tolerance. We conducted a large, prospective, multicenter, phase III randomized trial with a weekly regimen of high-dose leucovorin and FU infusion administered during an 8-hour period to patients with advanced colorectal cancer. We compared patients who received a constant dose of FU based on body-surface area (arm A) with those who received an individualized pharmacokinetically guided, dose-intensified, FU-based treatment (arm B).^{12,20} The primary efficacy end point was tumor response; the secondary end point was treatment tolerance.

PATIENTS AND METHODS

Patients

Patients from five hospitals that were treated for measurable metastasis of an adenocarcinoma of the colon or the rectum, with a pathologically confirmed diagnosis in first-line therapy, were eligible to participate in the study. All patients had to have measurable metastasis. Of those patients, some could have a local recurrence associated to the metastasis. Any adjuvant chemotherapy had to have been completed at least 6 months before enrollment in

the trial. Lesions were measured according to Response Evaluation Criteria in Solid Tumors Group criteria on a computed tomographic (CT) scan, an ultrasound of a liver lesion, or a CT scan of a pulmonary or other lesion. Lesions could not have been treated with radiotherapy and had to measure ≥ 10 mm (lung) or ≥ 20 mm (liver, soft tissue masses). Ascites and pleural effusions were not considered measurable. Patients were required to have a performance status (PS) ≤ 2 according to the WHO classification, a life expectancy of at least 3 months, and adequate hematopoietic function.

Patients were not eligible if they were pregnant or lactating, were older than 85 years, or had a history of other malignancy except for cured basal cell carcinoma of the skin or in situ cervical carcinoma. Patients were also considered ineligible if they had a neurologic or psychiatric disorder, or a cerebral metastasis of their disease that could interfere with treatment compliance, significant cardiac disease or a myocardial infarction within the previous 12 months, or serious uncontrolled infections. Patients were not enrolled if screening evaluations revealed significant abnormalities in hematopoietic function, such as neutrophils less than $1.5 \times 10^9/L$ and platelets less than $100 \times 10^9/L$. The trial protocol was approved according to French law by the regional ethics committee. Informed written consent was obtained from all patients before they were enrolled onto the study.

Treatment

Treatment consisted of weekly 8-hour (9 AM to 5 PM) continuous infusions of FU in 1 L of serum with 0.9% saline via a battery-operated pump. Bolus leucovorin 200 mg/m² was administered just before and at hour 4 of the FU infusion, up to a total weekly dose of 400 mg/m². Leucovorin doses remained constant in the two arms for the remainder of treatment.

The patients were randomly enrolled in one of two arms. In arm A, the FU dose was 1,500 mg/m²/wk, and remained unchanged throughout the whole period except if toxicity necessitated a reduction in dosage. In arm B, the initial FU dose was 1,500 mg/m² and then was adjusted for each patient before every cycle, beginning with the second cycle. The dose adjustment was calculated based on the results of weekly plasma concentration measurements, following a FU dose-adjustment algorithm (Table 1).^{12,20,24}

FU Dosage Adjustment

In arm B, the FU doses were adjusted weekly until the patients reached the therapeutic plasma range (2.5 to 3 mg/L; AUC 20-24 mg·h·L⁻¹). In two previous studies, patients with FU plasma levels at steady-state lower than 2.5 mg/L (AUC < 20 mg·h·L⁻¹) were underdosed and failed to respond to treatment, whereas patients with plasma concentrations > 3 mg/L (AUC > 24 mg·h·L⁻¹) were at high risk of severe adverse toxic effects.^{12,20} Therefore, we established a dose-adjustment chart based on pharmacokinetic follow-up with FU concentrations measured at hour 3 and hour 7 of the infusion using a previously published technique (Table 1).²⁶ Duplicate plasma assays were

Table 1. FU Dose Adjustment as a Function of FU Plasma Levels Recorded During the Previous Cycle of Treatment

In the Absence of Toxicity			In the Presence of Toxicity*
FU Plasma Concentration ($\mu\text{g/L}$)	AUC (mg·h·L ⁻¹)	FU Dose Adjustment (\pm % of previous dose)	
< 500	< 4	+70	Grade II toxicity: dose decreased by 200 mg Grade III toxicity: 1 week break, then dose decreased by 300 mg
500-1,000	4 to < 8	+50	
1,000-1,200	8 to < 10	+40	
1,200-1,500	10 to < 12	+3	
1,500-1,800	12 to < 15	+20	
1,800-2,200	15 to < 18	+10	
2,200-2,500	18 to < 20	+5	
2,500-3,000	20 to < 24	Unchanged	
3,000-3,500	24 to < 28	-5	
3,500-3,700	28 to < 31	-10	
> 3,700	> 31	-15	

Abbreviations: FU, fluorouracil; AUC, area under the curve.

*Using the WHO grade scale.

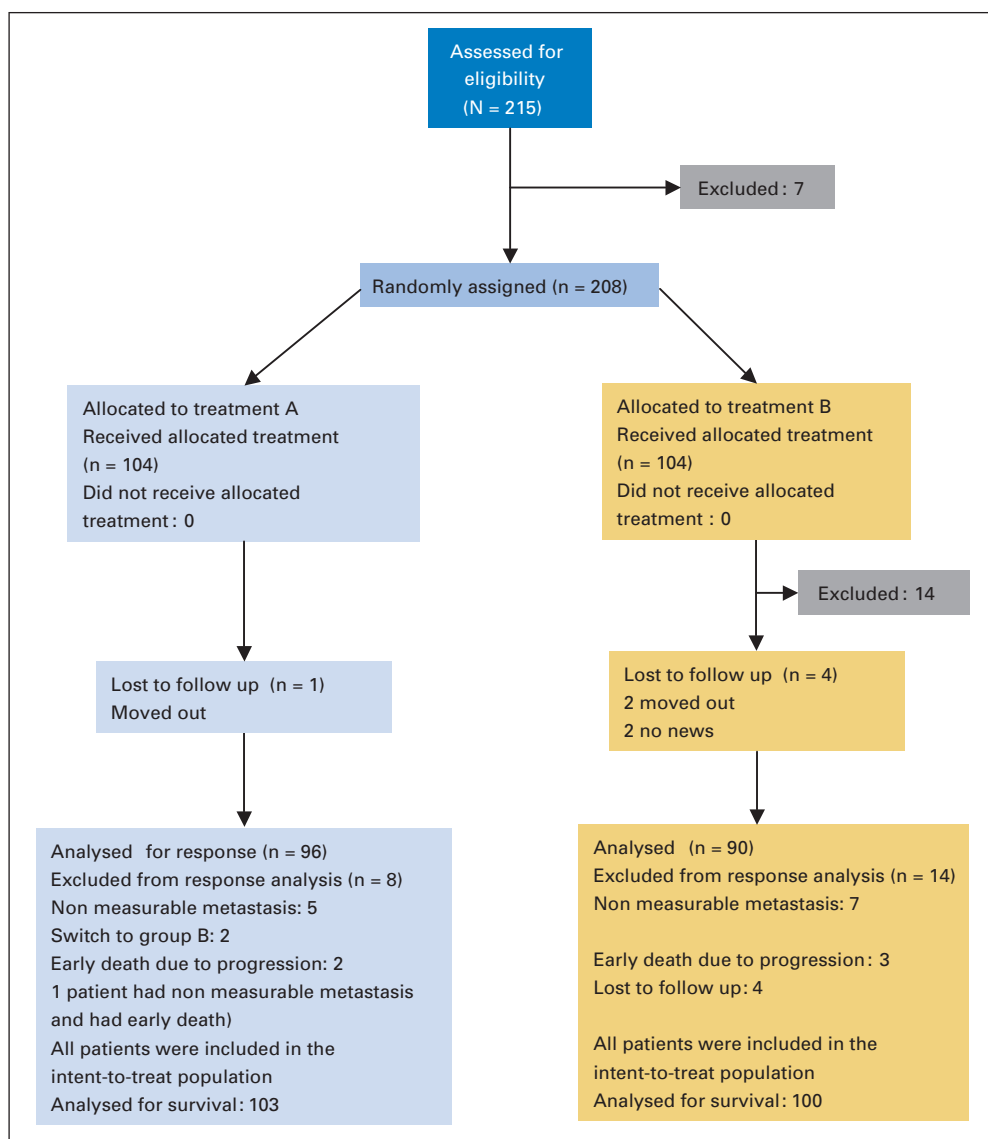


Fig 1. CONSORT diagram.

performed to avoid errors and erroneous dose-adjustment recommendations because of FU infusion rate variations. A medical oncologist made the final dose recommendation based on the assessment of the patient's clinical status and treatment tolerance. After target plasma concentration levels were maintained for at least three cycles, plasma measurements could be reduced to once every 3 weeks. Proficiency testing (accuracy and precision) was performed biannually under the quality control test program of the Clinical Pharmacology Group of the French Federation of Anticancer Centers.

Follow-Up

Patients underwent weekly physical examinations. Evaluation of treatment response was performed in patients enrolled in arm A after 15 weekly cycles of treatment, and in patients enrolled in arm B after 12 weekly cycles in which therapeutic target levels had been reached (it generally took three cycles to reach target levels). Treatment efficacy assessment was based on a comparison of tumor measurements before and after 3 months of treatment. Treatment continued until progressive disease, or intolerable toxicity, or the patient declined treatment.

Assessment of Response

Assessment of tumor response, the primary efficacy end point, was performed at 3 months after the initial treatment and then every 2 months.

Measurable disease was defined as the presence of a lesion that could be bidimensionally measured by CT scan or echography. Response to treatment was classified according to Response Evaluation Criteria in Solid Tumors Group criteria. A panel of two independent radiologists reviewed the CT scans of all patients. A complete response 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 (SD) required lesion size decrease of less than 50%. Progressive disease (PD) categorization encompassed any situation in which any one lesion increased in cross-sectional size by more than 25% or a new lesion appeared. Duration of treatment and OS were characterized.

Assessment of Tolerability

Patients were assessed before each weekly cycle using the National Cancer Institute Common Toxicity Criteria. Hemogram, and urea, and creatinine tests were performed every month. In the event of a significant grade 2 toxicity (principally diarrhea, hand-foot syndrome, or mucositis), the dose was reduced by 100 mg/m². In the case of grade 3 toxicity, treatment was stopped until the toxicity was reduced and then restarted with a 250 mg/m² decrease in dosage. Treatment was terminated in cases of grade 4 toxicity, and the case was reported to the French Drug Committee.

Table 2. Patient Characteristics Before Treatment

Characteristic	Arm A	Arm B
No. of patients	104	104
Sex		
Male	65	61
Female	39	43
Age, years		
Mean	71.2	71.5
Standard deviation	10.3	9.5
Range	50-85	52 to 84
No. of previous adjuvant chemotherapy	16	11
Performance status, %		
0	55	54
1	40	33
2	5	13
3-4	0	0
No. of assessable patients	96	90
Nonassessable patients, n		
Nonmeasurable metastasis	5	7
Life span < 3 months	2	3
Treatment crossover	2	
No. of patients lost to follow-up	1	2
Metastatic sites (measurable), %*		
Liver	74	81
Lung	30	26
Lymph nodes	11	19
Others	9	15
Different metastatic sites per patient, %		
1	77	68
2	21	24
3	1	6
4	0	2
Metastases, n		
1 to 3	26	16
3 to 10	46	43
> 10	27	40
Local recurrence, %	8	4

*Percentage of patients.

Table 3. Phase III Randomized Trial: Response to Fixed FU Dose (Arm A) Versus Individual FU Monitoring (Arm B)

Characteristic	Arm A	Arm B
Efficacy, No. of patients		
CR	1	6
PR	17	29
SD	30	26
PD	48	39
<i>P</i>		.0004
Mean duration of response, months		
CR		10
PR	6.3	6.8
SD	5.7	7.6
Performance status, %		
Improved	7.6	11.1
Stable	53.8	61.8
Worsened	37.6	26.9
Liver metastasis resection, No.	8	11
Overall survival, %		
Mean at 1 year	48.5	67.5
Standard deviation	11	10
Mean at 2 years	12.6	27.5
Standard deviation	9	10
<i>P</i>		.08

Abbreviations: FU, fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Statistical Study

Given an objective response rate of approximately 17% with FU plus folinic acid in metastatic colorectal cancer, the estimated percentage of 31% with a pharmacokinetic follow-up, and assuming a 5% type I error rate and 80% power, 95 patients per arm were required. We considered that 10% of patients would not be assessable. Thus the final number of patients required per arm was 104.

All statistical analyses were performed using SPSS software (SPSS Inc, Chicago, IL). χ^2 test and Fisher's exact test were used for comparison of different frequencies. Kaplan-Meier estimates and log-rank test were employed in univariate analysis of OS and time to treatment.

The Cox regression method was used for toxicity risk multivariate analysis. The same method was used for response to FU-based treatment or OS and progression-free survival multivariate analysis. The Kaplan-Meier method was used to describe the survival curve, and the log-rank test was used to compare curves (Fig 1).

RESULTS

Patient Characteristics

Two hundred eight patients (82 female and 126 male) were enrolled onto the study. Of these, 186 patients—96 and 90 in arms A

and B, respectively—were evaluated. Their mean age was 70.9 ± 0.75 years (range, 44.6 to 84.6 years). The patients' characteristics are summarized in Table 2, and are well balanced between the two arms.

Of the total patient population, 55% had several metastatic sites (42% and 58% in arms A and B, respectively). The most frequent metastatic sites were liver (77.6%), lung (27.3%), and lymph nodes (14.7%). Additionally, 12 patients had local disease recurrence, and 67 had 10 or more metastatic sites. Twenty-seven patients had prior chemotherapy treatment with FU plus folinic acid, with a mean delay of 14.6 months.

Twenty-two patients were not assessable. Despite the inclusion criteria, 12 patients had nonmeasurable disease (five in arm A and seven in arm B); five patients had a life span of less than 3 months (two in arm A and three in arm B); and two in arm A had cross-over treatments. Three patients were unaccounted for. All patients were included in the intent-to-treat population.

Treatment Characteristics

Ninety-six of the patients enrolled in arm A were fully assessable. The median duration of treatment was 7.5 months (range, 0.4 to 24.3 months). Ninety of the patients enrolled in arm B were assessable. The time-to-treatment evaluation in 68% of the patients in arm B was shorter than in arm A if the patient reached and maintained FU drug levels in the pharmacokinetic therapeutic range for 2 months (eight cycles). Median duration of treatment in arm B was 8.2 months (range, 1.2 to 31.5 months).

Response to Therapy

Results of the response to therapy were evaluated in the intent-to-treat population, and nonassessable patients were systematically

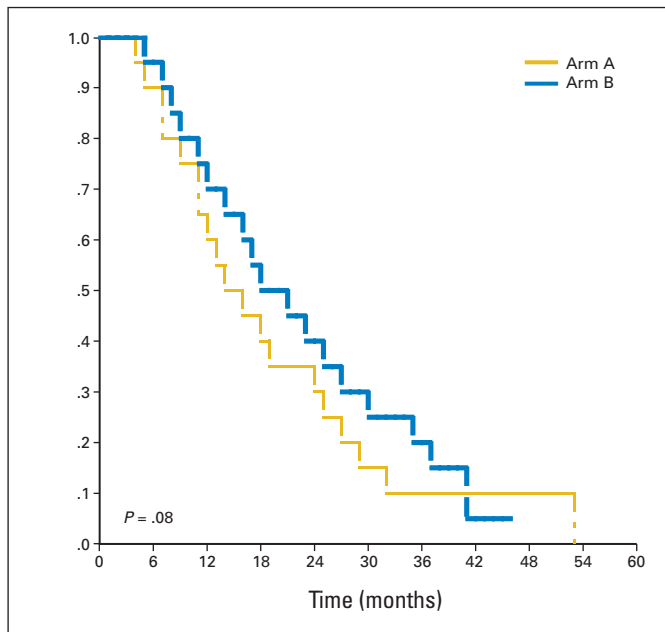


Fig 2. Survival curve comparison: standard arm (arm A) versus pharmacokinetically guided, fluorouracil dose-adjusted arm (arm B).

classified into PD groups. In arm A, one patient had a complete response, 17 patients had a PR (17.3% objective response), 30 patients had stable disease (28.8%), and 48 had PD (plus nonmeasurable disease, 53.8%). Mean duration of response was 6.3 months in cases of PR, and 5.7 months in cases of SD. Of the 96 patients, 7.6% had an improved PS evaluated according to the WHO classification; 53.8% had a stable PS, and 37.6% had deteriorated PS. Eight patients had surgical resection for secondary liver metastasis (Table 3).

In arm B, six patients had a complete response (5.8%), 29 patients had a PR (27.8%), 26 patients had SD (25%), and 29 patients had a PD (41.3%). The mean duration of response was 10, 6.8, and 7.6 months for complete response, PR, and SD, respectively. Ten patients (11.1%) had an improved PS (evaluated according to the WHO classification), 61.8% had stable PS, and 26.9% experienced a worsened PS. Eleven patients had a residual-metastasis surgical resection after treatment evaluation.

In terms of therapeutic efficacy, the overall response rate was 18.3% for arm A and 33.6% for arm B ($P = .0004$). The OS rate after 1 year was $59.5\% \pm 11$ in arm A and $70.5\% \pm 10$ in arm B. After 2 years, the OS rate was $29.6\% \pm 9$ (arm A) and $40.5\% \pm 10$ (arm B; $P = .08$; Fig 2). Median OS was 16 months in arm A and 22 months in arm B.

Tolerance

Toxic events are listed in Table 4. Diarrhea and hand-foot syndromes were the most frequent toxic events and occurred mainly during the first 3 months of treatment. Toxicity was significantly more prevalent in arm A compared with arm B, regardless of the time of treatment ($P = .003$). Treatment in arm A was continued with a decrease in FU dosage in 24 patients, postponed in 30 patients (for a mean of 8 days, and a maximum of 1 month), and discontinued in one patient.

Pharmacokinetic Study

In arm B, the FU therapeutic range was reached in 94% of patients, and a mean of four cycles (range, one to 10 cycles) was required to achieve the target concentration. The dosage necessary to achieve the target FU plasma levels differed greatly between populations (Fig 3). In arm B, the mean dosage after 3 months of treatment was $1,790 \text{ mg/m}^2/\text{wk}$ (range, 765 to $3,300 \text{ mg/m}^2$). In arm A, a dose of $1,500 \text{ mg/m}^2$ was administered to all patients. Plasma levels also were

Table 4. Percentage of Types and Grades of Toxic Events Observed for the First 3 Months and Throughout Treatment

Toxicity, %	First 3 Months of Treatment, WHO Grade				Whole Treatment,* WHO Grade			
	I	II	III	IV	I	II	III	IV
Diarrhea								
Arm A	14	27	14	0	14	28	15	3
Arm B	9	3	4	0	9	3	4	0
Mucositis								
Arm A	2	1	1	1	2	1	1	1
Arm B	2	0	0	0	2	1	1	1
Hand-foot syndrome								
Arm A	14	17	2	0	16	22	7	0
Arm B	13	17	2	0	30	21	10	1
Leukopenia								
Arm A	0	2	1	1	0	2	1	1
Arm B	0	0	0	0	0	0	0	0
Cardiac toxicity								
Arm A	1	1	1	0	1	1	1	0
Arm B	0	0	1	0	0	0	1	0
Conjunctivitis								
Arm A	11	3	0	0	11	5	0	0
Arm B	21	2	0	0	21	2	0	0

*Whole treatment: arm A, 680.6 months; arm B, 791.7 months.

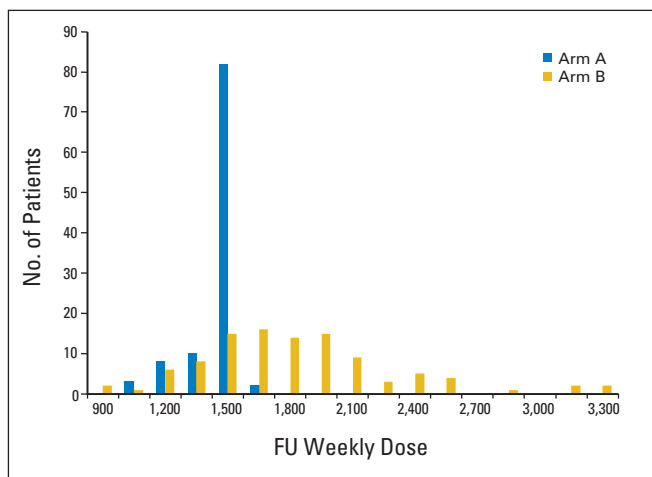


Fig 3. Dosage required to achieve target fluorouracil (FU) plasma levels in arm B versus dosage administered in arm A at 3 months of weekly treatment.

determined in 49 patients in arm A, and only four out of 49 patients had plasma levels in the therapeutic range. One of these four patients was in PR, and three were in SD. A relationship between FU plasma levels and objective response rate was found ($P = .004$).

A close link was found between acute toxicity (diarrhea and hand-foot syndrome) and FU plasma levels. Plasma levels between 2.5 and 3 mg/L were correlated with grades 1 and 2 diarrhea and grade 1 hand-foot syndrome. Grade 3 diarrhea and hand-foot syndrome were significantly linked with FU plasma levels more than 3 mg/L (3.5 and 3.9 mg/L, respectively; $P = .02$).

DISCUSSION

A significant body of data supports a close relationship between FU concentration in plasma, and tolerance and efficacy. Pharmacokinetically guided, FU dose adjustment has previously been tested to predict dose, avoid severe toxic adverse effects, and allow safe dose-intensification, but with the advent of new drugs it has not been sufficiently investigated in advanced colorectal cancer.^{12,13,20-25} Some major questions remain. Can we prevent the 20% of grade 3-4 adverse toxic effects usually reported with FU⁴? Can we still use FU alone, as suggested by two randomized studies? If that is the case, how can we individually optimize the management of this drug in a routine practice?

In a previous large, prospective, multicenter phase II trial in colorectal cancer, we reported that dose intensification by means of pharmacokinetic monitoring resulted in a high 38% response rate.¹² The goal of the current phase III study was to demonstrate the value of this approach in terms of efficacy, tolerance, and survival. With a median follow-up of 3 years, we confirmed the concept of individual FU dose management, and demonstrated that it not only increased the efficacy and the safety of chemotherapy, but also was easily applicable in clinical routine practice. A 33% overall objective response was observed in arm B, which was significantly higher than the 18% response with FU monotherapy without dose adjustment. It is noteworthy that the response rate in arm A was equivalent to those previously reported in the literature, regardless of the schedules.⁴ Likewise, the median OS was 22 months. This efficacy was nearly equivalent to

those currently reported with combined regimens, which are associated with considerably more toxicity and financial cost.^{5,6,27} The incidence of toxicity in the group of patients with dose monitoring was very low. We can assume that FU pharmacokinetic monitoring is an equivalent gain in terms of efficacy as that of an added cytotoxic drug, but without the toxic adverse effects. Furthermore, two recent multicenter randomized clinical trials comparing one versus two drugs in first-line therapy demonstrated no substantial difference in OS and treatment duration in the combined group, and more importantly, the combined group showed a higher toxicity than the one-drug group.^{7,8} Thus, in first-line therapy, except for selected patients such as those with potentially resectable or curable metastatic disease, patients could benefit from FU plus folinic acid alone, provided that FU administration is optimized. This could spare other drugs for future lines and increase the OS, as hypothesized by Grothey,²⁹ who reported a correlation between the number of lines of chemotherapy and the OS, with a well-tolerated regimen and a low cost.

We also found a wide pharmacokinetic variability and a large distribution of the optimal dose to achieve the same therapeutic plasma range. Five patients were found to be in the toxic range after the first dose, warranting a quick and marked reduction of the next dose to less than 1,000 mg/m². With no dose adjustment, these patients—with an obvious dihydropyrimidine dehydrogenase deficiency—would have been at high risk for toxicity under a conventional regimen.^{15,16,28} However, for some patients the dose necessary to maintain optimal plasma levels changed throughout the treatment period.

We have demonstrated in practice that we can manage FU administration to optimize therapy on an individual basis. Plasma-level measurement of FU with a single point at steady-state concentration is the optimal means for ensuring appropriate dose-intensity for improved outcomes while minimizing toxicity, and can be done more effectively and safely than by clinical dose adjustment. It can be easily integrated into routine clinical practice, regardless of the regimen, whether given alone (eg, leucovorin and fluorouracil), or combined (eg, infusional fluorouracil, leucovorin, and oxaliplatin, and fluorouracil, leucovorin, and irinotecan; data not shown).⁴⁻⁶

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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