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Modeling the 5-Fluorouracil Area Under the Curve Versus Dose Relationship to Develop a Pharmacokinetic Dosing Algorithm for Colorectal Cancer Patients Receiving FOLFOX6

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ABSTRACT

Background. **5-Fluorouracil (5-FU) is administered based on standard body surface area (BSA) dosing. BSA administration results in highly variable exposure, measured as the area under the concentration-time curve (AUC). An immunoassay (OnDose®; Myriad Genetic Laboratories, Inc., Salt Lake City, UT) that measures plasma 5-FU concentration and reports an AUC in mg · h/L has been developed to optimize therapy using pharmacokinetic (PK) dosing. The results of an analysis to model the 5-FU AUC-dose relationship are presented.**

Methods. **A set of 589 sequential patients from a clinical database receiving 5-FU, leucovorin, and oxaliplatin (the FOLFOX6 regimen) for colorectal cancer (CRC) treatment was analyzed. A subset including only patients who had at least two consecutive cycles tested, received 1,600–3,600 mg/m^2 of continuous infusion 5-FU during the initial test cycle, and had a blood sample collected after ≥18 hours, was used to conduct regression modeling of the change in AUC versus change in dose.**

Results. **A simple regression model with $R^2 = 0.51$ developed over $n = 307$ cycle-pair observations characterizes the AUC-Dose relationship as: change in AUC = 0.02063 * dose change. The model suggests that dose changes in the range of 145–727 mg/m^2 would be sufficient to adjust the AUC to a potential therapeutic threshold of >20 mg · h/L for most patients.**

Conclusions. **5-FU is an ideal candidate for PK dose optimization. Because individual factors other than dose change may also affect the change in AUC, longitudinal PK monitoring in all cycles and dose adjustment to ensure AUC in the desired range of 20–30 mg · h/L are recommended.** ***The Oncologist*** 2012;17:296–302

INTRODUCTION

In the treatment of cancer patients with cytotoxic drugs, a prime consideration is improving the therapy outcome by increasing efficacy while maintaining an acceptable toxicity profile. Thus, fine tuning of chemotherapy needs to consider the generally wide interindividual pharmacokinetic (PK) variability of such drugs and the finding that general toxicity and efficacy are more related to systemic exposure than to dose and dose intensity [1–3]. 5-fluorouracil (5-FU), which has been used in the treatment of a variety of solid tumors, is a prime example of this concept [4, 5].

5-FU has been the cornerstone of colorectal cancer (CRC) therapy since the 1960s, with regimens having undergone a series of modifications in order to enhance the benefits to pa-

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tients, ranging from enhanced monotherapy to multiagent polychemotherapy including irinotecan and oxaliplatin, and more recently, the addition of the targeted agents bevacizumab and anti–epidermal growth factor receptor antibodies. There has been a progressive improvement throughout the years in survival outcomes for these patients, but 5-FU has remained the cornerstone and the most important component of these regimens.

Like other chemotherapeutic drugs, 5-FU is generally characterized by a narrow therapeutic index and a large interindividual PK variability that has a direct effect on both toxicity and efficacy [4, 5]. Regardless of the regimen and schedule in which 5-FU is used, the method of dosing 5-FU in standard practice has not changed for decades and is based on the traditional use of body surface area (BSA). Although BSA dosing is convenient and easy to use, a number of studies have shown it to underestimate or overestimate exposure and clearance in the majority of patients treated, because there is no correlation among plasma clearance, exposure, and BSA. Studies have shown a very high level of variability in the exposure and clearance of 5-FU, suggesting the potential for underdosing of a significant proportion of patients and some greater risk for toxicity because of overdosing [6]. Sequential measurements of 5-FU area under the concentration-time curve (AUC) along cycles in a commercial database have also shown a wide distribution in exposure, with subsequent nonuniform dose changes resulting in a narrowing of the AUC distribution [7]. This 5-FU PK variability is affected by various factors, such as genotype, age, gender, disease state, drug–drug interactions, and organ function, as well as other not well-quantified factors. Of particular concern is the potential for underdosing of obese patients, which can adversely influence the treatment outcome in this rapidly growing part of the U.S. population [8–9]. Additionally, the effect of BSA dose calculation may lead to underdosing as a result of the practice of "dose capping" because of fear of overdosing [10].

One of the most significant a priori contributors to this PK variability of 5-FU has been the heterogeneity of the activity of the enzyme responsible for the metabolism of 5-FU, dihydropyrimidine dehydrogenase [11]. However, this accounts for a small minority of patients with a rare pharmacogenetic disorder, and the majority of the 5-FU PK variability occurs a posteriori after the drug has been administered, as shown in a study by Adjei et al. [12]. That study systematically confirmed the inherent inter- and intrapatient PK variability of 5-FU in serial measurements in patients receiving continuous i.v. 5-FU. Contrary to expectations, that study also showed that 5-FU concentrations do not seem to reach steady state until about 18 hours into the infusion.

Measurements of systemic exposure of 5-FU, such as the AUC, have been shown to correlate with toxicity, tumor response, and survival outcomes [13–17]. Most of these studies suggest that better responses occurred in patients with a mean 5-FU AUC in the range of 20–30 AUC units (mg · h/L) [13, 18]. Patients with 5-FU AUC below this level are receiving suboptimal therapeutic doses and those with 5-FU AUC above this range are at a greater risk for toxicity [19–21]. A higher response rate (39% versus 19%) and longer median overall survival (OS) time (22 months versus 16 months) were demonstrated in a phase III randomized trial comparing PK-guided dosing with a target AUC of 20–25 mg · h/L with conventional BSA dosing of infusional 5-FU [22]. Thus, the administration of 5-FU is an ideal candidate for personalizing dosing using individual PK parameters as a guide for optimizing therapy. AUC has been demonstrated to be the pharmacokinetic parameter that is most closely associated with efficacy and toxicity. Attempts at finding the right balance of maximizing exposure while limiting toxicity have been published, with favorable data, and indicate that there is a potential for optimizing 5-FU administration.

This retrospective analysis of PK data from a commercial laboratory setting is the first attempt to define a dose adjustment algorithm for 5-FU for the 5-FU, leucovorin, and oxaliplatin (FOLFOX6) regimen based on experience with infusions in a U.S. CRC patient population.

Methods and Patients

5-FU AUC Measurement

Plasma samples collected from patients were shipped to Myriad Genetic Laboratories, Inc. (Salt Lake City, Utah) for analysis. In the laboratory, the samples are filtered by spin column with a 100-kDa cutoff and the filtrate is used for the analysis. 5-FU measurement is performed using the OnDose® (Myriad Genetic Laboratories, Inc., Salt Lake City, UT) assay, a competitive homogeneous two-reagent nanoparticle agglutination immunoassay. The first reagent contains 5-FU conjugate with the second reagent consisting of 5-FU–directed antibody-conjugated nanoparticles. The amount of free 5-FU in the plasma inhibits aggregation of the two assay reagents. The amount of light absorbance at certain wavelengths from the nanoparticle agglutination depends on the amount of drug in plasma. This absorbance is compared with a standardized calibration curve for quantization. This method was adapted, developed, and crossvalidated at Myriad Genetic Laboratories, Inc., from a technique that previously had been validated against liquid chromatography–tandem mass spectrometry. The quantitative target range for 5-FU exposure, as expressed by the AUC, is calculated from the measured concentration of 5-FU and the infusion duration using standard methods.

Patients

Anonymized patient data were gathered from the commercial database (Myriad Genetic Laboratories, Inc.) from information entered on the test request forms for the 5-FU immunoassay (OnDose®). The following information was collected for this analysis: gender, age, pathological diagnosis of CRC, date of infusion, type of treatment (metastatic or adjuvant), type of infusional therapy (FOLFOX; 5-FU, leucovorin, and irinotecan; bevacizumab, other), total dose for infusion, duration of infusion, and time of sample draw from start of infusion.

Description of Analysis Datasets

The OnDose® test database has >3,000 observations (AUC measurements) from >1,300 patients in the U.S. clinical setting.

These patients have been referred by >500 physicians from various academic institutions, as well as community oncology practices, from 48 states. Because the data were collected from limited information submitted on test request forms in a commercial setting, there are data issues, such as missing values, as well as information gaps, such as a lack of information regarding the exact reasons for dose change decisions.

The above database is very heterogeneous, containing observations from different indications, a variety of 5-FU–containing regimens, and different infusion modalities. A fairly homogeneous analysis dataset is needed to effectively analyze the effects and relationships of interest. Therefore, the database was queried to generate a preliminary analysis dataset of 1,221 observations from 589 patients receiving the FOLFOX6 regimen with continuous infusion 5-FU, with or without bevacizumab, for the adjuvant or metastatic treatment of CRC.

The initial aim was to evaluate the effects of sample collection time on AUC measurements, in order to identify the optimal blood draw time for PK analysis. For most (96%) of the observations in the dataset, the collection times are distributed around three sample collection time modes: the beginning of infusion (@2 hours), the middle of infusion (@22 hours), and toward the end of infusion (@44 hours). As such, a restricted analysis dataset of 1,172 observations from 572 patients was derived from the preliminary analysis dataset of 1,221 observations by removing the few observations with collection times in between these three modes. Extreme AUC outlier values (>50 mg · h/L) were removed, because these might be related to sampling directly from the i.v. port or in proximity to it.

A critical requirement for developing any dosing algorithm is to model the change in AUC versus the change in dose relationship. A longitudinal dataset with AUC measurements from at least two consecutive cycles for each patient is needed for such modeling. In the above preliminary analysis dataset of 1,221 observations, many patients had only a single AUC measurement, whereas some others had more than one measurement but not at consecutive infusion cycles.

Therefore, from the preliminary analysis dataset, a smaller longitudinal modeling dataset was identified with the following characteristics: (a) the patient had AUC measurements for at least two consecutive infusion cycles with a dose change, (b) the 5-FU dose received during the initial test cycle was 1,600–3,600 mg/m^2, (c) the blood sample collection times were ≥18 hours from the start of the 5-FU infusion for each cycle (based on the findings from the collection time analyses), and (d) outliers such as AUC values <5 mg · h/L and >50 mg · h/L were excluded.

A "cycle-pair observation" consists of measurements from two consecutive infusion cycles for the same patient. So, a patient with AUC measurements at only two consecutive infusion cycles would provide one cycle-pair observation for these analyses, whereas a patient with AUC measurements at four consecutive infusion cycles would provide three cycle-pair observations. In addition to meeting the above criteria, for each cycle-pair observation to be included in the modeling dataset, the patient needed to have a dose change between the two consecutive infusion cycles. The resulting modeling dataset consists of 307 cycle-pair observations from 187 patients.

Table 1. Area under the concentration–time curve (AUC) summary statistics by collection time mode

Collection time mode	*n*	Mean (mg · h/L)	Standard Deviation (mg · h/L)	*p*-value versus @2 hours	*p*-value versus @22 hours
@2 hours	101	16.8	6.80	NA	.0003
@22 hours	396	20.2	7.36	.0003	NA
@44 hours	675	20.6	9.33	<.0001	.5178

Abbreviation: NA, not applicable.

The difference in AUC between the two measurements constituting a cycle-pair observation provides the "change in AUC" in mg · h/L, whereas the corresponding difference in 5-FU dose amount provides the "change in dose" in mg/m^2. A simple regression analysis was then used to model the change in AUC (mg · h/L) versus the change in dose (mg/m^2) relationship.

Results

Effect of Sample Collection Time on AUC Measurement

The effects of sample collection time on AUC measurements were evaluated in an analysis dataset of 1,172 single observations. The mean AUC measurements were compared among three collection time modes using a simple analysis of variance model with AUC measurement as the dependent variable and collection time mode as the factor (Table 1). The mean 5-FU AUC level was significantly lower when the blood sample was drawn in the early hours of the infusion. This low mean value is likely caused by a variety of factors, including varying rates of 5-FU metabolism before steady-state conditions are reached and sampling before the pump was fully primed with drug.

The statistically significant lower mean AUC value at the 2-hour collection time mode indicates the existence of large variability in 5-FU PK measurements during the early part of the infusion cycle. Consequently, the analysis dataset used for modeling the AUC versus dose relationship was restricted to observations with sample collection times ≥18 hours after the start of the infusion, when there is less variability (Fig. 1).

Modeling the 5-FU AUC Versus 5-FU Dose Relationship

The modeling of change in AUC versus change in 5-FU dose relationship was conducted on a longitudinal modeling dataset consisting of 307 cycle-pair observations from 187 patients.

Patient Characteristics

One hundred eighty-seven patients (104 male and 79 female) receiving FOLFOX6 with or without bevacizumab were included in the analysis (Table 2). The mean age was 58.2 years.

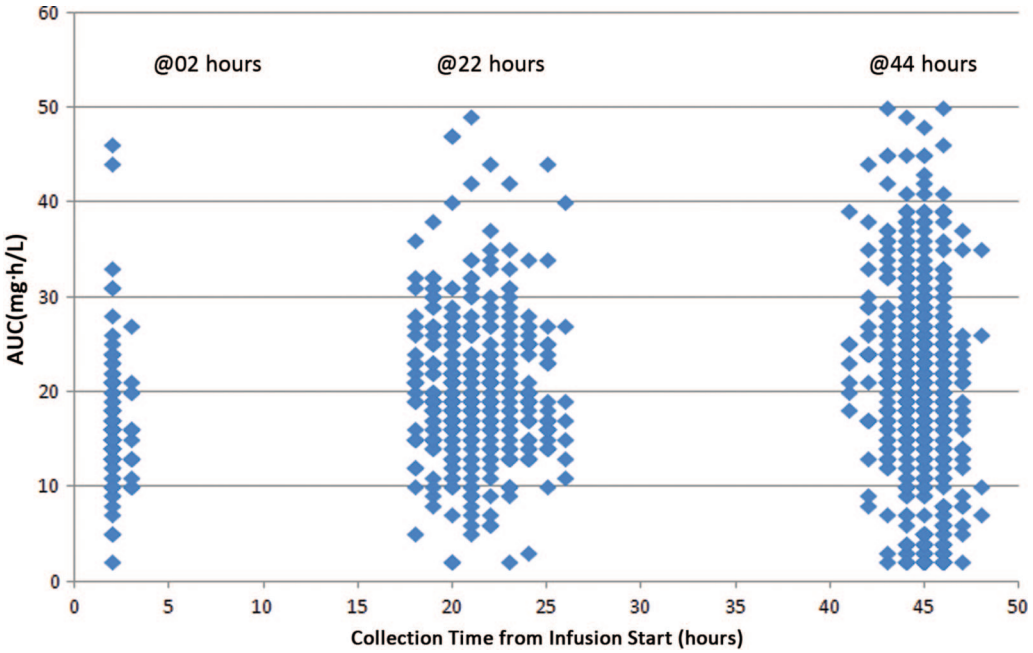

Figure 1. Distribution of area under the concentration–time curve (AUC) by collection time mode.

Table 2. Patient summary statistics

Characteristic	*n* (%) of patients (*n* = 187)
Gender	
Male	104 (56.8%)
Female	79 (43.2%)
Missing	4
Age, yrs (*n* = 181)	
Mean	58.2
Standard deviation	11.71
Minimum–maximum	27–88
Type of regimen	
FOLFOX6 + bevacizumab	67 (35.8%)
FOLFOX6	120 (64.2%)
Treatment type	
Metastatic	118 (63.8%)
Adjuvant	67 (36.2%)
Missing	2

Abbreviation: FOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.

Patient characteristics are summarized in Table 2. FOLFOX6 without bevacizumab was the therapy for 120 patients (64.2%), and bevacizumab was added to the regimen for 67 patients (35.8%). One hundred eighteen patients (63.8%) had metastatic disease, and 67 patients (36.2%) were treated with an adjuvant intent. Some patients had missing values for one or more of these variables.

Cycle-Pair Characteristics

Of the 307 cycle-pairs identified in the test cohort (Table 3), 109 patients (58.3%) had one cycle-pair, 46 patients (24.6%) had two cycle-pairs, 22 patients (11.8%) had three cycle-pairs, and 10 patients (5.3%) had four cycle-pairs. The baseline mean dose was 2,263.4 mg/m^2 (standard deviation [SD], 457.42 mg/m^2), and the baseline mean AUC was 20.2 mg · h/L (SD, 8.5 mg · h/L). The mean absolute dose change was 268.0 mg/m^2 (absolute SD, 192.56 mg/m^2) and the mean absolute change in AUC was 6.9 mg · h/L (absolute SD, 6.53 mg · h/L).

Paired observations (n = 307) were selected as described above to examine the change in AUC versus change in dose relationship. A regression model with R^2 = 0.51 characterized the AUC–dose relationship as: change in AUC (mg · h/L) = 0.02063 * dose change (mg/m^2) (Fig. 2).

5-FU Dose Adjustment Based on Prior AUC Reading

Using the AUC–dose relationship calculated above, a dose adjustment table was generated to provide a practical application of the AUC measurement in modifying the subsequent dose in order to bring exposure to the desired level (Table 4).

A Proposed Dose Adjustment Algorithm

Using the previous cycle 5-FU AUC value, it is suggested that one can use Table 4 in order to calculate the increase or decrease in the next 5-FU dose to achieve the desired 5-FU AUC at the next cycle. However, for feasibility and adaptability in a real clinical setting, a dose adjustment algorithm is proposed for use in a clinically relevant dose range (Table 5). Based on commercial testing experience (>3,000 tests), it has become obvious that the proposed target range of 20–24 mg · h/L in the literature is too narrow (a range of

Table 3. Cycle-pair summary statistics

Cycle-pair characteristic	*n* (%) of cycle-pairs (*n* = 307)
n of cycle-pairs per patient	
1	109 (58.3%)
2	46 (24.6%)
3	22 (11.8%)
4	10 (5.3%)
Baseline dose (mg/m^2)	
Mean	2,263.4
Standard deviation	457.42
Minimum–maximum	1,600–3,600
Baseline AUC (mg · h/L)	
Mean	20.2
Standard deviation	8.50
Minimum–maximum	5–50
Dose change (mg/m^2)	
Mean (absolute)	268.0
Standard deviation (absolute)	192.56
Minimum–maximum	−1,000–1,177
Change in AUC (mg · h/L)	
Mean (absolute)	6.9
Standard deviation (absolute)	6.53
Minimum–maximum	−33–32

Abbreviation: AUC, area under the concentration–time curve.

only 4 mg · h/L units) to be useful in the presence of the variability in 5-FU PK readings. This algorithm suggests using a 20–30 mg · h/L target range. The lower limit of 20 mg · h/L was considered valid based on published efficacy data [13, 18, 22]. However, the upper limit of 24 mg · h/L was generated using more toxic regimens of 5-FU administration and may not be considered relevant for the less toxic newer regimens. The upper limit of 30 mg · h/L is supported by published data and is thus recommended as an upper limit of target exposure [15, 20, 21, 23]. Consequently, the width of the proposed target range is 10 mg · h/L, a range wide enough to realistically accommodate the intrapatient 5-FU PK variability, thus reducing the need for frequent and unnecessary dose adjustments.

Discussion

This analysis models a relationship that provides an algorithm that allows dose changes to be dialed up or down, based on PK parameters, to be within an optimal therapeutic range. The data indicate that dose changes in the range of 291–727 mg/m^2 would be sufficient to adjust the AUC to a potential therapeutic threshold of >20 mg · h/L for most patients receiving FOLFOX6 with or without bevacizumab. Patients given doses that result in AUC values under this threshold have a higher risk for underdosing, with lesser efficacy. The analysis also provides an upper threshold for potential greater toxicity. Assuming a 2,400 mg/m^2 baseline dose, a maximum 727 mg/m^2 dose increase would correspond to a 30% increase and would be needed only by patients who have an initial AUC measurement ≤10 mg · h/L. Previously published analyses using the same commercial database show that only 10.4% of the patient population had such low initial AUC measurements at that dose level [7].

The data for this study come from a commercial testing database, rather than a controlled clinical trial. However, this is the largest dataset of this type from a real-world clinical setting in the U.S. This provides a certain degree of robustness to the analysis results. A large efficacy trial to test the utility of this dose adjustment algorithm is currently ongoing.

Dose adjustment algorithms based on 5-FU AUC have been reported for some 5-FU–containing regimens, such as weekly 8-hour infusion regimens with concomitant leucovorin [20], long-term 5-FU with or without cisplatin [17], and a bimonthly regimen of i.v. 5-FU with a bolus infusion and a continuous infusion over the next 22 hours on two consecutive days [19]. Effective individualized dose management of 5-FU in the treatment of CRC patients was demonstrated in phase II and phase III trials. In a study of 152 CRC patients treated weekly with 1,300 mg/m^2 5-FU (8-hour infusion) and with 400 mg/m^2 leucovorin, the weekly dose was adapted based on a dose adjustment chart to reach a predefined plasma concentration range of 2–3 mg/L (AUC_8, 16–24 mg · h/L). This dose adjustment strategy was associated with both superior efficacy and better tolerability than with conventional BSA dosing [14].

This individualized dose optimization method was compared with conventional BSA 5-FU infusion in a phase III randomized trial of 208 CRC patients with a target AUC of 20–25 mg · h/L [22]. In that study, 70% of patients required adjustment of their doses in order to achieve the optimal therapeutic dose. Of these, >58% of patients required an increase in dose, with 10%–20% requiring a dose reduction in order to have an AUC within the optimal range. That trial demonstrated a higher rate of complete and partial responses (39% versus 19%; $p = .0004$). The median OS times were 16 months for patients in the BSA arm and 22 months for patients in the PK arm ($p = .08$). Toxicity was seen in more patients receiving BSA dosing than PK dosing ($p = .003$). Successful dose adjustment was achieved in 94% of the patients. Only 8% of patients receiving BSA dosing were found to have an AUC within the optimal range.

The above studies clearly demonstrate that CRC therapy with 5-FU–containing regimens is suited to therapeutic drug monitoring and a posteriori dose adjustment based on individualized determination of PK parameters. However, the data in these trials were generated using 5-FU monotherapy and dose ranges that have currently been improved to include other agents and use a more prolonged administration of 5-FU. One of the most recent iterations of combination chemotherapy for CRC is FOLFOX6 containing oxalipatin and leucovorin with

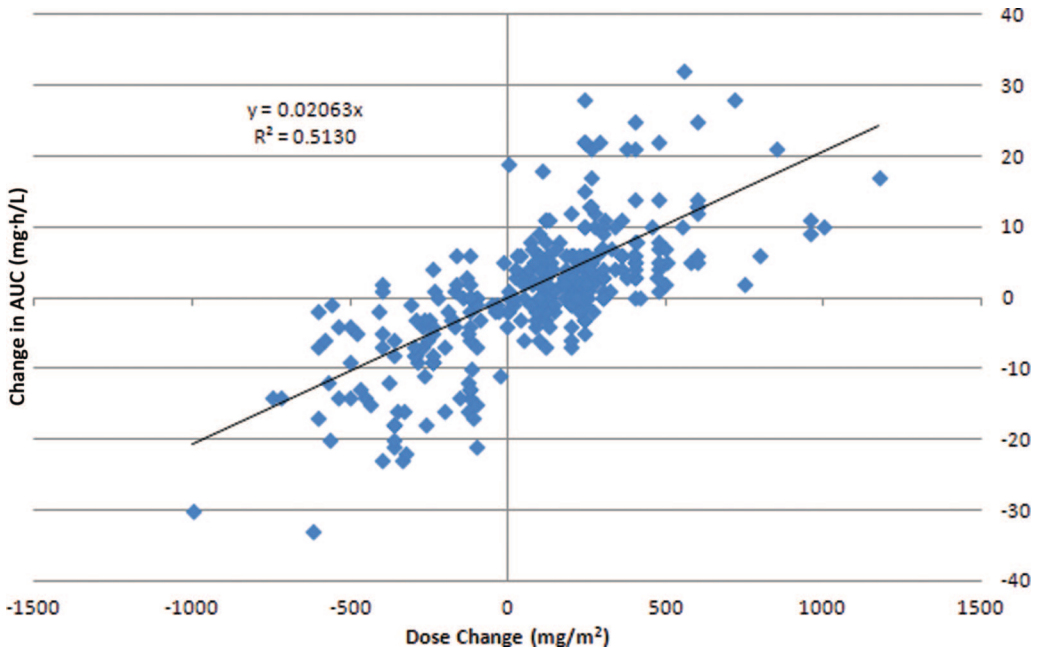

Figure 2. Change in 5-fluorouracil dose versus change in 5-fluorouracil area under the concentration–time curve (AUC) relationship.

Table 4. Dose adjustment table

Change in AUC (mg · h/L)	Change in dose (mg/m^2)
±15	±727
±13	±630
±11	±533
±9	±436
±7	±339
±5	±242
±3	±145

Abbreviation: AUC, area under the concentration–time curve.

Table 5. Proposed dose adjustment algorithm

AUC (mg · h/L) from previous cycle	Change in dose (mg/m^2)
≥40	↓ 727
37–39	↓ 582
34–36	↓ 436
31–33	↓ 291
20–30	**No change needed**
17–19	↑ 291
14–16	↑ 436
11–13	↑ 582
8–10	↑ 727

Abbreviation: AUC, area under the concentration–time curve.

or without bevacizumab. In that regimen 5-FU is administered as a bolus of 400 mg/m^2 and a continuous infusion of 2,400 mg/m^2 over 46 hours. This prolonged administration of 5-FU is associated with less 5-FU–related toxicity. The analysis presented in this paper and the suggested dose adjustment algorithm take into account this greater tolerability of 5-FU with this regimen, and in combination with data from the literature suggest an optimal AUC range of 20–30 mg · h/L [22, 23]. The analyses of the dose–exposure relationship reveal that it is possible to optimize the dose of 5-FU based on previous PK determination and provide a practical guideline and a tool to reach optimal target exposure levels by making modest adjustments so that subsequent doses are within the desired range. PROFUSE (PROspective 5-FluoroUracil OnDoSe® Evaluation), a large controlled clinical trial to test the utility of this dose adjustment algorithm versus standard BSA dosing, is currently ongoing in the U.S. (ClinicalTrials.gov identifier, NCT01468623) [24]. It is expected that positive efficacy results from this trial would lead to greater adoption of PK-guided 5-FU dosing in the U.S.

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