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## Pharmacokinetic adaptation of 5-fluorouracil: where are we and where are we going?

“...using the traditional body surface area calculation method, 43% of patients were not given the right dose: 33% were underdosed (significantly reduced efficacy) and 10% were overdosed (running a strong risk of severe early-onset toxicity).”

**KEYWORDS:** 5-FU ■ colorectal cancer ■ dose adjustment ■ fluoropyrimidines ■ personalized medicine ■ pharmacokinetic ■ PK ■ TDM ■ toxicity

### Taking into account human heterogeneity to improve treatment tolerance & efficacy

Personalized medicine is fast becoming the new paradigm in treatment management in oncology resulting in improved drug efficacy, avoidance of severe toxic reactions and reduction of health-care costs by giving the right drug at the right dose to the right patient.

Without question, many important advances have been made with regards to treatments tailored to tumor characteristics; however, it is wise to remember that determining the proper therapeutic approach has as much to do with the patient's metabolism as with the tumor itself. It is the wide interpatient variability in the metabolism of certain chemotherapy drugs that has been the focus of groundbreaking progress in therapeutic drug monitoring (TDM) using pharmacokinetics (PKs).

This is especially true for cytotoxic anticancer drugs, and in particular, 5-fluorouracil (5-FU). 5-FU is used in the treatment of over 50% of solid tumors (including colorectal, head and neck, stomach and pancreatic cancer). It has been the cornerstone of the treatment of colorectal cancer since the 1960s, and is still included today in all major chemotherapy regimens (monotherapy, FOLFOX [leucovorin, fluorouracil and oxaliplatin], FOLFIRI [leucovorin, fluorouracil and irinotecan], FOLFIRI–cetuximab and panitumumab, among others).

The good news is that awareness in the oncology community is growing fast now that the superiority of TDM approaches have been proven, time and again. There are now new tools available to facilitate the adoption of 5-FU treatment individualization and optimization in clinical practice.

### Dose calculation: from body surface area obsolescence towards new efficient TDM–PK methods

Since the 1950s, body surface area (BSA) has been used to calculate the dosage of many drugs, but in the case of 5-FU, this method has no scientific basis, and can often lead to error.

5-FU is a prime candidate for PK-guided dose adjustment because it has quite a narrow therapeutic range. It is not a simple matter to reach the correct concentration during infusion due to its nonlinear PKs, resulting in wide inter- and intra-individual variability. It is very clear that BSA dosing very often leads to either underdosage or overexposure, since studies have shown that there is no correlation between plasma clearance and BSA [1].

In 1998 Gamelin *et al.* showed that using the traditional BSA calculation method, 43% of patients were not given the right dose: 33% were underdosed (significantly reduced efficacy) and 10% were overdosed (running a strong risk of severe early-onset toxicity) [1].

The variability in plasmatic clearance is due, in part, to polymorphisms in the gene coding for the enzyme DPD, as well as other individual parameters. These parameters taken together can be considered the source of a potentially serious DPD deficiency, which if not taken into account in dosing strategies, can cause severe multiorgan toxicities (lethal in 0.3% of patients). It is very important to note that DPD activity levels can be screened before starting treatment, using a multiparametric approach combining genotyping, phenotyping, and physiological and pathological parameters integrated into algorithms (i.e., ODPM Tox™, Onco Drug Personalized Medicine [ODPM], Angers, France).



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### Origins of research into PK-guided 5-FU adaptation

From as early as 1989, different teams were already publishing studies showing the strong correlation between 5-FU concentration, therapeutic efficacy and toxicity [2–6]. Since the 1990s, many authors have shown that 5-FU is subject to nonlinear PKs and that there are significant interindividual variations. Another study found a coefficient of variation of interpatient steady-state concentrations of 15–20% [7]. In other studies, significant correlations were found between toxicity and steady-state concentration or area under the curve (AUC) of 5-FU [8]. During continuous intravenous administration, higher AUC was correlated significantly with leukopenia, mucositis, diarrhea and hand–foot syndrome [1,9]. Many studies have been published investigating the impact of therapeutic monitoring on the effectiveness of 5-FU regimens. For example, in studies where 5-FU was used alone, the AUC >24,000 mg/hl<sup>-1</sup> correlated with an improved objective response rates [1,10].

### PK-guided treatment intensification: proof of concept

A randomized study published in the *Journal of Clinical Oncology* in 2008, showed for the first time the impact of therapeutic optimization of 5-FU PK monitoring in terms of objective response and progression-free survival [11]. In this study, 208 patients with metastatic colorectal cancer were randomized into two arms treated with combination 5-FU and folinic acid infused 8-h weekly.

“The reliability of these algorithms has been proven through over 90,000 cycles of chemotherapy (over 14,000 patients) as well as in published studies.”

In arm A, patients received the standard (BSA) dose of 5-FU and in arm B, the dose in each cycle was adjusted pharmacokinetically. The average doses (mean ± standard deviation) of administered 5-FU were 1500 mg/m<sup>2</sup>/week (arm A) versus 1790 ± 386 mg/m<sup>2</sup>/week (range: 900–3300 mg/m<sup>2</sup>/week; arm B). The results showed a significant difference in objective response between the two arms, with 46.1% in the nonadapted arm (arm A) versus 58.6% in the PK-guided arm (arm B).

Similarly, overall survival rates were higher in arm B, at 1 year (48.5 vs 67.5%) and at 2 years (12.6 vs 27.5%). Drug tolerability was also better in arm B compared with A (6 vs 22% severe

toxicities reported, respectively) with an improved overall performance status throughout treatment.

In another study using a more common protocol (FOLFOX, 46-h infusion), the same team has shown that the overall response rate was much better in the PK-adapted arm versus the standard one (mg/m<sup>2</sup>; 69.7 vs 46.6%) [9]. These results are similar to the response rates shown in many of the more costly tritherapies; whereas, in the study by Gamelin *et al.*, dose adjustments were calculated using only the observed AUC of 5-FU [11]. In the study by Capitain *et al.*, additional parameters (e.g., genotype, phenotype, physiological, physiopathological and associated treatments, among others) were integrated into the optimized algorithms (ODPM Tox<sup>TM</sup> and ODPM Protocol<sup>TM</sup>, ODPM) used to adapt the dosages [9]. Another study goes even further, showing that by using PK-guided dose adaptation of 5-FU, as well as irinotecan in a FOLFIRI–cetuximab protocol, the control of the disease exceeded 70% (overall response 33% and stable disease 39%) without any grade 4 toxicities, even though certain patients would have been at risk for toxicity to 5-FU or irinotecan without pretreatment screening and subsequent dose adaptation [12]. This study clearly shows that PK-guided dose adaptation gives patients at risk of early-onset toxicity to 5-FU, who would have otherwise not have been treated with 5-FU at all, the opportunity to respond to treatment, even with a reduced dose recommendation, and have similar encouraging treatment outcomes to patients given higher doses.

### Where are we today? Simple techniques in clinical practice

The proof of the 5-FU therapeutic individualization concept is well established and these practices have been common in France for over 15 years. The techniques are relatively easy to implement in the hospital setting. The standard procedure is to measure 5-FU plasma concentration from a sample drawn during continuous infusion. Since 5-FU is catabolized by lymphocytic DPD present in whole blood, the sample (collected in a lithium-heparinized tube) has to be centrifuged immediately after collection [13]. The 5-FU in plasma is stable for 48 h, beyond which the sample must be frozen. The assay can be performed using either plasma or serum. Different techniques have been published [14,15]. The clinician will then base the adjustment of the subsequent dose on the plasma concentration found in the sample (AUC) – adjusting upwards if the concentration is too low, downwards if too high.

### What's next? Putting it all in place

I would like to use this article to state clearly that clinicians must be aware of two important facts regarding the algorithms published in 2008. The first is that the treatment (8-h weekly infusion) is not widely used. The second, and the most important, is that the algorithms cannot be extrapolated to fit any other protocol (any other infusion duration or associated molecules) due to the nonlinear nature of 5-FU metabolism; to do so would be to endanger the patients under our care. The algorithms have been, and continue to be, optimized using many other factors, adapted to current protocols, and have been made available worldwide as ODPM Protocol™. The reliability of these algorithms has been proven through over 90,000 cycles of chemotherapy (over 14,000 patients) as well as in published studies.

Clinicians must beware of overly simplistic algorithms with unproven therapeutic range assumptions and that only take into account the 5-FU AUC. Indeed, the use of this insufficient approach may result in significantly reduced treatment efficacy or worse, serious toxicities

that could have been foreseen using other techniques.

The most important task before us is to do everything we can to change clinical practice, continue to convince oncologists that this 'old' molecule, when administered at the correct dosage, can be as efficient as the newer, trendier treatments, while remaining far less expensive and, on the whole, safer for the patient, resulting in an improved quality of life during treatment. This improved method of patient care is based on a close collaboration between clinician, nurse and laboratory personnel (who have solely an advisory role, while the clinician remains in ultimate control of their patient's treatment).

### Financial & competing interests disclosure

*M Boisdron-Celle is co-founder and president of ODPM. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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