Received: 22 October 2020 | Revised: 9 December 2020 | Accepted: 14 December 2020

DOI: 10.1002/psp4.12590

PERSPECTIVE

# Mechanistic models for hematological toxicities: Small is beautiful

**There is a rising trend to implement algorithm-based tools for precision oncology. Several strategies are available, ranging from complex approaches to simpler phenomenological models. Whereas complex models can help understanding the underlying cellular or molecular mechanisms, phenomenological models are merely descriptive. Conversely, such simple models are the most likely to reach bedside application because of their simplicity. It is critical to balance the pros and cons of each strategy for precision medicine in real-world settings.**

Developing mathematical models to describe pharmacodynamic end points with anticancer drugs is a rising strategy in precision medicine in oncology. For instance, an analysis aiming at characterizing resonance (i.e., neutrophil oscillations) in young patients treated by cyclic chemotherapy has been recently presented.[1] Complex quantitative systems pharmacology (QSP) modeling applied to granulopoïesis was used to demonstrate that timing of chemotherapy could impact the dynamics of neutrophils. This kind of work suggests that model-informed scheduling could help limiting hematological toxicity, for example, by delaying supportive granulocyte colony-stimulating factor (G-CSF) therapy, thus eventually improving clinical outcomes at the bedside. The issue of controlling drug-induced adverse events, especially hematological toxicities with cytotoxics, is critical in many respects. Pancytopenia can be rapidly life-threatening, especially in frail patients. When they do not directly lead to toxic death, such severe toxicities frequently oblige practitioners to postpone or discontinue chemotherapy or associated radiation therapy, thus eventually affecting clinical outcomes and survival. Altogether, developing strategies to control or reduce the risk of drug-induced hematological toxicities is therefore a major concern in clinical oncology, especially because cytotoxics are still today the backbone of most treatments of solid tumors and hematological malignancies. Developing in silico approaches as decision-making tools to optimize anticancer therapies has been a rising trend for decades in clinical oncology.[2] Pharmacokinetically guided regimens with Bayesian adaptive dosing procedures have been already proposed for several years to tailor the administration of a variety of cytotoxics and oral-targeted therapies.[3] However, implementing adaptive dosing strategies in routine clinical settings remains challenging. Real-world precision medicine requires mathematical models that are kept simple enough to allow proper identification of their parameters. This is a prerequisite for being easily applied prospectively in actual patients and not to be used solely as part of retrospective in silico modeling. This calls for using primarily top-down approaches, such as compartmental analysis, before developing pharmacokinetics/pharmacodynamics (PK/PD) models likely to help oncologists determine the optimal dosing and scheduling of a given drug to a given patient. More intricate modeling and QSP approaches are appealing strategies that are unfortunately impaired by their intrinsic complexity, which has made them unfit for routine use at the bedside so far (Figure 1). The complexity of a model should fit to the data made actually available to infer unknown parameters, thus ensuring to make meaningful predictions. When the dimensionality of a model is too large, such predictions are practically intractable because they are associated with large uncertainty. Nevertheless, QSP models might be more appropriate to specific problems, especially if they involve measurable physiological parameters that can be extrapolated, for example, from animals to humans such as for determining the first-in-human dose of immune checkpoint inhibitors such as anti-PD1 pembrolizumab.[4] In addition, they offer mechanistic insights that help develop a quantitative understanding of complex pharmaco-patho-physiological processes. Conversely, phenomenological modeling could in many respects look like an oversimplistic, suboptimal strategy, often mocked as being "black boxes" simply linking an output to a given input. However, such models have demonstrated their utility in real-world settings, not despite the fact that they are black boxes, but precisely because they are black boxes.[5] For instance, the Friberg model is a simplified representation of hematopoiesis using a semimechanistic, compartmental description of the proliferation and dynamics of the maturation of blood progenitors.[3] Because of its smart

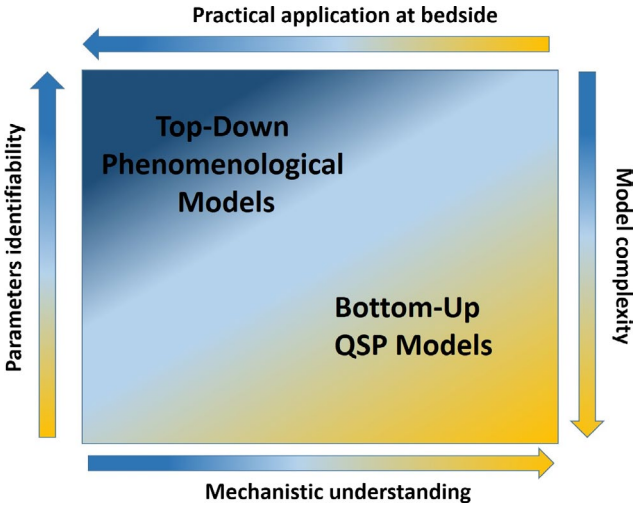


**FIGURE 1** Pros and cons of complex versus simple models in clinical oncology. QSP, quantitative systems pharmacology

simplicity, this top-down approach has allowed the Friberg model to be extensively used during the past 15 years both by academics and pharmaceutical companies to describe the myelosuppressive effects of a variety of cytotoxics. Countless phenomenological models have been derived from the Friberg model ever since. For instance, the Meille model is based on a similar simplified and semimechanistic representation of hematopoiesis and granulopoiesis, which encapsulates additionally a PK/PD model describing effects of supportive G-CSF administration on blood cell progenitors.[6] When further combined with another phenomenological model for antiproliferative efficacy, it was used next to build an original constraint model determining the optimal dosing and scheduling of densified chemotherapy combo plus G-CSF support. Once calibrated with predefined acceptable levels of hematological toxicity and desired level of tumor shrinkage, this mathematical-driven regimen was finally tested prospectively in patients with metastatic breast cancer and showed excellent performances such as prolonged overall survival in heavily pretreated patients with fully controlled hematological toxicities.[7] Importantly, the prospective use of such a mathematical model was only made possible because of a first parameters identification step from few blood samples taken at baseline, thus providing individual data on drugs PK profile and blood counts. This critical step allowed the fine tuning of individual PK/PD model parameters in real time, thus ensuring optimal, personalized dosing. Transposing such a model-driven regimen at bedside seems to be only achievable when the whole modeling strategy is primarily built on the parsimony principle so as to be able to identify the next individual parameters from sparse, routine data collected from patients in a real-world setting. Among other examples, model-driven adaptive dosing strategies have been successfully implemented in routine bedside practice with several canonical cytotoxics, such as cisplatin, carboplatin, or methotrexate.[5] For instance, with the alkylating agent carboplatin, Bayesian-adaptive dosing was compared with a priori dosing charts using standard Calvert or Chatelut formulas, both based on renal clearance estimation. Results showed that it was possible to increase up to 60% carboplatin dosing when using a simple PK model compared with a priori dosing strategies without triggering toxicities and without the use of growth factors in real-world, unselected patients.[8] This highlights how real-time and dynamic adaptive dosing strategies can yield substantial benefits compared with a posteriori use of a mathematical algorithm to define a priori the dosing in a given patient. Of note, no in-depth understanding of biological mechanisms can be provided by such models—the dosing and scheduling of anticancer agents and G-CSF are connected to efficacy and toxicity end points through phenomenological black boxes, not by using multiscale models providing biological explanations of the observed phenomenon. In contrast, QSP models offer appealing mechanistic features, thus allowing a better understanding of all the underlying mechanisms at play to explain pharmacodynamic end points. The downside is that such models are complex. They are frequently based on dozens of parameters, a large number of them being fixed from literature data and thus are dependent on the variability and/or possible biases of the experiments used for their very identification.[9] Furthermore, in contrast to standard approaches in pharmacometrics using nonlinear mixed effects modeling, interindividual variability of the parameters is often not quantified. The issue with so many parameters is that the practical identifiability from sparse individual data collected at bedside is expected to be poor, resulting in uncertainty in quantitative model predictions in real-world practice.

Nevertheless, the qualitative observation of the resonance effect in neutrophil time dynamics induced by the administration of periodic chemotherapies should prompt modelers to include such pivotal phenomena, including in their phenomenological representations of hematological toxicity. Altogether, a rising number of studies highlight how the very way we use anticancer agents does matter, and how the same drug can have diametrically different PD effects depending on its scheduling. In this respect, all of these works are important contributions to the field of precision medicine in oncology, suggesting that there is much room left to improve the standard use of canonical cytotoxics and that upfront in silico strategies could help better administer anticancer drugs.[9,10] To transform this theoretical concept into a practical decision-making tool for oncologists, mathematicians and modelers must first fix the issue of parameters identifiability in clinical practice, and what kind of accessible individual data are made available in real-world, routine patients. If these issues are not fixed, modeling will unfortunately remain for the years to come an elegant but theoretical field of research disconnected from bedside practice. To the ever-rising complexity

of cancer biology and the amazing amount of knowledge regarding the in-depth mechanisms of action of drugs (such as molecular signaling pathways, genetic and epigenetic regulations affecting targets, or key proteins involved in PD responses), the temptation to implement all of this knowledge into supermodels should be resisted. Models should rather be built in the perspective of future practical application. Indeed, for an efficient in silico–to–bedside transposition, we believe that the more complex is a phenomenon, the simpler should be the mathematical model describing it.

## CONFLICT OF INTEREST

The authors declared no competing interests for this work.

## FUNDING INFORMATION

No funding was received for this work.

Laure Deyme[1]
Sébastien Benzekry[2]
Joseph Ciccolini[1]

[1]*SMARTc Unit, Centre for Research in Cancer of Marseille, Inserm U1068, Aix Marseille Univ, Marseille, France*
[2]*Monc Team, INRIA Bordeaux Sud Ouest Institute for Mathematics of Bordeaux, CNRS, UMR 5251, Bordeaux University, Talence, France*

**Correspondence**
Joseph Ciccolini, SMARTc Unit, Centre for Research in Cancer of Marseille, Inserm U1068, Aix Marseille Univ, Marseille France.
Email: joseph.ciccolini@univ-amu.fr

## REFERENCES

1. Mackey M, Glisovic S, Pastore Y, Krajinovic M, Craig M. The timing of cyclic cytotoxic chemotherapy can worsen neutropenia and neutrophilia [published online ahead of print 2020]. *Brit J Clin Pharmacol*. https://doi.org/10.1111/bcp.14424
2. Barbolosi D, Ciccolini J, Lacarelle B, Barlési F, André N. Computational oncology–mathematical modelling of drug regimens for precision medicine. *Nat Rev Clin Oncol*. 2016;13:242–254.
3. Friberg LE, Henningsson A, Maas H, Nguyen L, Karlsson MO. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. *J Clin Oncol*. 2002;20:4713–4721.
4. de Greef R, Elassaiss-Schaap J, Chatterjee M, et al. Pembrolizumab: role of modeling and simulation in bringing a novel immunotherapy to patients with Melanoma. *CPT: Pharmacom Sys Pharmacol*. 2017;6:5–7.
5. Ferrer F, Fanciullino R, Milano G, Ciccolini J. Towards rational cancer therapeutics: optimizing dosing, delivery, scheduling, and combinations. *Clin Pharm Ther* 2020;108:458–470.
6. Meille C, Barbolosi D, Ciccolini J, Freyer G, Iliadis A. Revisiting dosing regimen using pharmacokinetic/pharmacodynamic mathematical modeling: densification and intensification of combination cancer therapy. *Clin Pharmacokinet*. 2016;55:1015–1025.
7. Hénin E, Meille C, Barbolosi D, et al. Revisiting dosing regimen using PK/PD modeling: the MODEL1 phase I/II trial of docetaxel plus epirubicin in metastatic breast cancer patients. *Breast Cancer Res Treat*. 2016;156:331–341.
8. Mercier C, Ciccolini J, Pourroy B, et al. Dose individualization of carboplatin after a 120-hour infusion schedule: higher dose intensity but fewer toxicities. *Ther Drug Monit*. 2006;28:212–218.
9. Craig M, Humphries AR, Mackey M. mathematical model of granulopoiesis incorporating the negative feedback dynamics and kinetics of G-CSF/neutrophil binding and internalisation. *Bull Math Biol*. 2016;78:2304–2357.
10. Wallin JE, Friberg LE, Karlsson MO. Model-based neutrophil-guided dose adaptation in chemotherapy: evaluation of predicted outcome with different types and amounts of information. *Basic Clin Pharmacol Toxicol*. 2010;106:234–242.