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ORIGINAL ARTICLE

# Impact of granulocyte colony-stimulating factor on FOLFIRINOX-induced neutropenia prevention: A population pharmacokinetic/pharmacodynamic approach

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**Aims:** Granulocyte colony-stimulating factor (G-CSF) is frequently prescribed to prevent chemotherapy-induced neutropenia, but the administration schedule remains empirical in case of bimonthly chemotherapy such as FOLFIRINOX regimen. This pharmacokinetic/pharmacodynamic (PK/PD) study was performed to determine the effect of different G-CSF regimens on the incidence and duration of neutropenia following FOLFIRINOX administration in order to propose an optimal G-CSF dosing schedule.

**Methods:** A population PK/PD model was developed to describe individual neutrophil time course from absolute neutrophil counts (ANC) obtained in 40 advanced cancer patients receiving FOLFIRINOX regimen. The structural model considered ANC dynamics, neutropenic effect of cytotoxics and the stimulating effect of G-CSF on neutrophils. Final model estimates were used to simulate different G-CSF dosing schedules for 1000 virtual subjects. The incidence and duration of neutropenia were then calculated for different G-CSF dosing schedules.

**Results:** The final model successfully described the myelosuppressive effect induced by the 3 cytotoxics for all patients. Simulations showed that pegfilgrastim administration reduced the risk of severe neutropenia by 22.9% for subjects with low ANC at the start of chemotherapy. Median duration in this group was also shortened by 3.1 days when compared to absence of G-CSF. Delayed G-CSF administration was responsible for higher incidence and longer duration of neutropenia compared to absence of administration.

**Conclusion:** The PK/PD model well described our population's ANC data. Simulations showed that pegylated-G-CSF administration 24 hours after the end of chemotherapy seems to be the optimal schedule to reduce FOLFIRINOX-induced neutropenia. We also underline the potential negative effect of G-CSF maladministration.

KEYWORDS

adverse drug reactions, modelling and simulation, oncology, population analysis

The authors confirm that the Principal Investigator for this paper is Prof. François Ghiringhelli and that he had direct clinical responsibility for patients.

  

## 1 | INTRODUCTION

Nowadays, the efficacy of FOLFIRINOX regimen, combining **5-fluorouracil** (5-FU), **leucovorin**, **irinotecan** and **oxaliplatin**, is no longer to be demonstrated in metastatic colorectal cancer (mCRC) and advanced or metastatic pancreatic cancer.[1–4] Nevertheless, chemotherapy-induced neutropenia (CIN) is 1 of the most common dose-limiting toxicities of this combination.[5] Patients presenting neutropenia are more susceptible to opportunistic infections and sepsis, which may result in various potentially life-threatening complications. Moreover, cytotoxic doses at subsequent cycles are often reduced or dose intervals are lengthened, reducing treatment effectiveness and thus potentially overall survival.[6,7] For these reasons, exogenous granulocyte colony-stimulating factor (G-CSF) is often used to prevent or reduce high grade neutropenia. Different recombinant-forms of exogenous G-CSF are commercially available: 2 daily administration drugs (**filgrastim**, lenograstim) and a single administration long-acting pegylated formulation drug (**pegfilgrastim**).

The most recent updates of the American Society of Clinical Oncology and European Organisation for Research and Treatment of Cancer guidelines advocated a risk threshold of approximately 20% of febrile neutropenia (FN) to consider routine administration of prophylactic G-CSF.[8,9] Regarding every-3-week and monthly neutropenic chemotherapies, it is recommended that the first administration of filgrastim and lenograstim should be carried out at least 24 hours after the end of cytotoxic chemotherapy not exceeding 14 days or 28 days of treatment respectively, while pegfilgrastim has a 1-per-cycle administration. However, to date, limited data exist regarding the prophylactic use of G-CSF administration in every-2-week regimens, incorporating infusional 5-FU.[10,11] Some studies have revealed approximately 50% of severe neutropenia[12–14] and about 20% of FN[15–18] with FOLFIRINOX regimen, nevertheless the absence of G-CSF administration consensus for this combination leads to empirical use of growth factors that might not be fully effective.

During recent decades, several useful semiphysiological pharmacokinetic–pharmacodynamic (PK/PD) models have been established to predict neutrophil time-course during chemotherapy.[19–24] However, those models are inappropriate to describe the effect of exogenous G-CSF. Consequently, some PK/PD models of daily and/or pegylated formulation recombinant G-CSF effect on neutrophil production have been subsequently proposed.[7,25–28]

The aim of our work was to develop a semi-mechanistic model able to describe the evolution of absolute neutrophil count (ANC) following FOLFIRINOX regimen and G-CSF administration in patients with gastrointestinal cancer. The model was subsequently used to simulate different G-CSF regimens during 2 FOLFIRINOX cycles in virtual subjects. Based on these simulations, incidence and duration of neutropenia were calculated and optimal G-CSF dosing schedules selected.

### What is already known about this subject

- To date, limited data exist regarding the prophylactic use of granulocyte colony stimulating factor (G-CSF) administration for every-2-week infusional 5-fluorouracil regimens. The absence of international recommendation leads to an empirical use of G-CSF that could be, in some situations, not fully effective for patients.

### What this study adds

- We propose, for the first time, a pharmacokinetic/pharmacodynamic model able to capture the neutropenic effect of 3 different cytotoxics and the stimulating effect of G-CSF, allowing determination of the optimal G-CSF dosing schedule in patients treated with FOLFIRINOX. We have shown that nonoptimal G-CSF dosing schedules could be more harmful than no G-CSF administration.

## 2 | METHODS

### 2.1 | Patients

Analyses were performed with the help of data obtained from a database covering patients diagnosed with mCRC or pancreatic metastatic cancer who received FOLFIRINOX regimen from September 2014 to May 2016 in Dijon's Cancer Centre (Centre Georges-François Leclerc, Burgundy, France). Even though FOLFOXIRI is an alternative protocol in mCRC, only the FOLFIRINOX regimen is dispensed at our centre in order to facilitate patient care. Patients were included in the study if they started a new line of chemotherapy with FOLFIRINOX ± biotherapy. All patients routinely underwent complete blood cell counts (CBC) as part of the chemotherapy protocol, consequently no informed consent was required to collect evolution of ANCs. Patient confidentiality was maintained, and analysis was performed in compliance with guidelines approved by our Institutional Review Board.

### 2.2 | Treatment schedules

Patients were treated according to a standard FOLFIRINOX regimen.[29,30] Typically, oxaliplatin (85 mg/m$^2$) was administered as a 2-hour infusion followed by 2-hour infusion of leucovorin (400 mg/m$^2$) concurrently with irinotecan (180 mg/m$^2$) over 90 minutes. At the discontinuation of these 2 products, 5-FU was given as a bolus (400 mg/m$^2$) then a 46-hour continuous intravenous infusion (2400 mg/m$^2$). Each cycle of therapy was repeated every

14 days. However, clinicians had the discretion to individually adapt any drug doses, in particular if severe toxicity was observed. If necessary, doses at subsequent cycles could be scaled. Most of patients were given G-CSF subcutaneously as a daily formulation (filgrastim/lenograstim at 5 μg/kg/d) or as pegylated formulation (pegfilgrastim at 6 mg). The choice of timing and duration of G-CSF administration was left to the clinician's discretion.

## 2.3 | Blood sampling

CBC were performed before the first cycle of chemotherapy (within 4 d), during the intercycle period and on the first day of subsequent cycle (D14) during the first 2 months of treatment. Intercycle sampling schedule depended on the treatment; ANC were collected on Day 5 (D5) and D10 in case of absence of G-CSF, the first and the last day of G-CSF administration or the first day of the pegylated G-CSF (peg-G-CSF) administration and D10. Additional CBC realized in case of fever >38.5°C or during any hospitalization were also collected for this study.

## 2.4 | Population PK/PD model

A population PK/PD model was developed from ANC data obtained over the first 4 chemotherapy cycles in all patients. ANC homeostasis and dynamics, PK of cytotoxic drugs as well as PK of G-CSF and peg-G-CSF were modelled simultaneously.

### 2.4.1 | PK model development

Since no G-CSF and peg-G-CSF concentrations were available, prior information about Melhem's model was used.[28] Moreover, because no PK data were collected in this study, individual chemotherapy concentrations were simulated based on previously published population PK (popPK) models of 5-FU,[31] oxaliplatin[32] and irinotecan/SN-38.[33] PK/PD prior parameters used for the study are summarised in Supporting Data. The 5-FU PK model was a 2-compartment model with a nonlinear clearance, whereas oxaliplatin PK consisted of a 2-compartment model with a linear elimination. As irinotecan is the prodrug of SN-38, the disposition the parent drug was described with a linear 3-compartment model and that of SN-38 was described with a linear 2-compartment model, with a first-order formation of SN-38. Because SN-38 is 100- to 1000-fold more cytotoxic than irinotecan,[34,35] only SN-38 plasma concentrations were considered in this study. All models were covariate-free and parameters were fixed to the population published values.

### 2.4.2 | PD structural model development

Proliferation and maturation of neutrophils were mimicked by a series of 5 compartments with the first representing the number of G-CSF receptors of the precursor cells coming from progenitors' differentiation [$R_{PROL}$], followed by 3 transit compartments mimicking G-CSF receptors of maturing granulocyte precursors [$R_{TR1-3}$] and the last characterising circulating mature neutrophil G-CSF receptors [$R_{CIRC}$]. The systematic turnover of proliferative cells production was modelled by a zero-order rate constant $k_{PROL}$ which reproduced the effect of endogenous G-CSF. The [$R_{CIRC}$] concentration, driven by first-order production and elimination rate constants, $k_{PROL}$ and $k_{CIRC}$ respectively, was divided by an estimated scaling factor (SF), which depicted cellular G-CSF receptor density, to transpose receptor concentrations into ANCs. Mean transit time (MTT), described as the average time for a cell to mature and appear in the systemic circulation, was defined as $MTT = (1 + n)/K_{TR}$, where $n$ is the number of transit compartments. Based on literature and to simplify our analysis, $n$ was fixed to 3.[24,27,36,37]

In this model, the effect of G-CSF depends on the concentration of free G-CSF or peg-G-CSF; therefore, the fraction of occupied G-CSF receptors over the total number of G-CSF receptors appears to be the driving force of G-CSF and peg-G-CSF effects on precursor production ($ST_1$) or precursor maturation ($ST_2$), with maximum stimulatory effects $STM_1$ and $STM_2$ respectively.

The drug-induced neutropenic effect ($E_{DRUG}$) was expressed as a linear function proportional to the drug concentration ($C_{DRUG}$) and a parameter representing the sensitivity to drug myelotoxicity ($SLOPE_{DRUG}$). Drugs effects were implemented separately on different sites of the neutrophil dynamics; the action of SN-38, active metabolite of irinotecan, is modelled as an inhibition of progenitor cells' proliferation, oxaliplatin exerts its cytotoxic activity directly on precursor cells, while 5-FU drug action is characterized by an inhibition of granulocytes precursors' maturation.

## 2.5 | Estimation model and software

Population PK-PD analyses were performed using nonlinear mixed-effect modelling within MONOLIX software (version 2018R2, Antony, France: Lixoft SAS, 2019). We applied logarithmic transformation to ANCs. Model parameters were estimated by the stochastic approximation expectation minimization algorithm with log-likelihoods estimated by linearization and standard errors by a stochastic approximation. A log normal distribution of individual PK/PD parameters was assumed, and residual error was modelled with an exponential component.

## 2.6 | Covariate analysis

All parameter–covariate relationships with a significant Pearson test $P$-value ($P < .05$) were added in a stepwise covariate approach. Models were evaluated and compared by the obtained Wald test $P$-value ($P$-value of .01 in forward addition), reduction of IIV parameters and precision of parameter estimates. Data collected routinely included sex, age, weight, height, body surface area, treatment line,

long-term corticosteroid therapy, serum creatinine, creatinine clearance, haemoglobin concentration, leucocyte, eosinophil and basophil counts, monocyte and platelet counts, proteinemia, albuminemia, uraemia, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, γ-glutamyl transferase, and total bilirubinaemia.

### 2.7 | Model evaluation

Selection of the final model was based on the physiological coherence and precision of parameter estimates, comparison between model objective function values (OFV) and graphical diagnostics including the observed *vs* predicted concentration plots, residuals plots and visual predictive checks (VPCs). Accuracy and robustness of estimated parameters were confirmed by a bootstrap method. Final model parameter estimates were compared to median and 90% confidence intervals of 200 repeated random sampling with replacement from the original dataset. VPCs were performed independently for each situation (no G-CSF, peg-G-CSF or G-CSF administration). One thousand data set replicates were simulated from the final model to produce VPCs.

### 2.8 | Simulations

Based on the final PK/PD model, simulations were performed to explore the optimal schedules of G-CSF and peg-G-CSF administration.

Firstly, 1000 ANC time-course simulations were performed at fixed doses for a standardized body surface area of 1.73 $m^2$ (i.e. 4844 mg of 5-FU, 311 mg of irinotecan and 147 mg oxaliplatin) without any G-CSF administration; simulated data were divided into a group of simulated individuals who experienced grade 0/I/II neutropenia and another group with grade III/IV neutropenia. Median baseline ANC was calculated for each group.

The 2 median values were then employed to define boundaries for 3 ranges of baseline ANC (high, moderate ant low initial neutrophils count) to simulate various G-CSF schedules. The R-package *mlxR* was used to generate 1000 individual neutrophils time-course simulations following FOLFIRINOX regimen administration and various G-CSF dosing schedule during 2 cycles. The incidence of all grade neutropenia and severe neutropenia (grade III/IV) as well as mean duration were then calculated for each G-CSF/peg-G-CSF regimen.

## 3 | RESULTS

### 3.1 | Patient population and treatment

From the 58 patients included, 18 did not have enough G-CSF information (type and dosing time) and only a few observed ANC were collected for them; therefore, they were excluded from the analysis. The final dataset comprised 342 ANC observations from the 40 patients remaining over a median duration of 50 days (i.e. 3.6 cycles). Only 1 patient did not receive G-CSF or peg-G-CSF, 30 patients received G-CSF and 9 patients received peg-G-CSF. Patient characteristics are summarized in Table 1.

### 3.2 | Final popPK/PD model

The final G-CSF/myelosuppression model is illustrated in Figure 1. Due to data sparseness, some PD parameters have been fixed according to literature values.[28] Only the following parameters were estimated: $K_{PROL}$ (nM/h), $K_{TR}$ ($h^{-1}$), $K_{CIRC}$ ($h^{-1}$), $STM_1$, $STM_2$, SF (nM/[× $10^9$/L]), $SLOPE_{FU}$ (L/mg), $SLOPE_{SN\text{-}38}$ (L/mg) and $SLOPE_{OX}$ (L/mg). Most model parameters were estimated with reasonable precision (relative standard errors [RSE] < 46%). Of note, RSEs for 3 parameters were in the range of 61.3–70.4%. A total of 189 out of 200 bootstrap runs reached successful convergence. Ratios of all parameters bootstrap median estimate/final parameter estimate were within a reasonable range of 70–152%. Estimated parameters and results of bootstrap analysis are presented in Table 2.

Estimated baseline ANC value was 5.61 × $10^9$/L and MTT was estimated to be 141 hours. Interindividual variability (IIV) was estimated for 4 parameters; better OFV and precisions of estimates have been obtained when only $SLOPE_{OX}$ variability was estimated compared to models considering $SLOPE_{FU}$ and $SLOPE_{SN\text{-}38}$ between-subject variability; therefore, only $SLOPE_{OX}$ IIV has been retained in the final model. During covariate analysis, we observed a parameter–covariate relationship between hepatic function parameters (aspartate aminotransferase and alkaline phosphatase) and sensitivity to myelotoxicity induced by FOLFIRINOX with Pearson test, but no covariate was retained since the model was not significantly improved when they were added to the structural model. Similarly, estimation of interoccasion variability and covariance among parameters were not statistically significant.

ANC individual fits, in randomly selected patients, showed that final model was able to adequately describe the ANC time-course after FOLFIRINOX regimen alone (Figure 2A), FOLFIRINOX regimen followed by G-CSF (Figure 2B) or peg-G-CSF (Figure 2C) administration. As observed in Figure 3, diagnostic plots demonstrated that both population- and individual-predicted ANC were well in line with observed ANC. Individual weighted residuals *vs* time and observed ANC were randomly and symmetrically scattered around the horizontal zero-line, indicating the absence of prediction bias, confirming structural model choice.

The final model was evaluated using VPC stratified by groups. Due to the small number of patients who did not receive G-CSF or who received peg-G-CSF, only VPC concerning G-CSF administration are interpretable. As shown in Figure 4, simulations for G-CSF treatment adequately matched observed data.

**TABLE 1** Summary of patients' characteristics

| | Median | Range |
|---|---|---|
| Demographic | | |
| Age (y) | 65 | [43–87] |
| Bodyweight (kg) | 67 | [42–100] |
| Height (cm) | 170 | [151–185] |
| Body surface area ($m^2$) | 1.78 | [1.40–2.11] |
| Laboratory tests | | |
| Haemoglobin (g/dL) | 12.6 | [9.6–16.3] |
| Neutrophil baseline ($\times 10^9$/L) | 5.69 | [2.15–11.78] |
| Platelets ($\times 10^9$/L) | 253 | [100–802] |
| Creatinine clearance (mL/min) | 92.4 | [50.0–155.9] |
| Chemotherapy doses at cycle 1 | | |
| Irinotecan (mg) | 320 | [68–380] |
| Fluorouracil (mg) | 4,900 | [3,850–5,900] |
| Oxaliplatin (mg) | 150 | [120–175] |
| ANC observations | | |
| Number observations/patient | 9 | 3–12 |
| G-CSF dosing information | | |
| Start of daily form after 1st d of CT (d) | 5 | 3–8 |
| Duration of daily form administration (d) | 5 | 3–7 |
| Start of pegylated form after 1st d of CT (d) | 5 | 3–8 |
| | Number of patients | Relative frequency (%) |
| Total no. of patients | 40 | 100 |
| Sex | | |
| Male | 23 | 57.5 |
| Female | 17 | 42.5 |
| Cancer location | | |
| Pancreas | 22 | 55.0 |
| Colorectal | 17 | 42.5 |
| Other | 1 | 2.5 |
| Biotherapy | | |
| No | 25 | 62.5 |
| Yes | 15 | 37.5 |
| Type of biotherapy (n = 15) | | |
| Bevacizumab | 13 | 86.6 |
| Cetuximab | 1 | 6.7 |
| Panitumumab | 1 | 6.7 |
| Line of treatment | | |
| 1st line | 26 | 65.0 |
| 2nd line | 4 | 10.0 |
| 3rd line or more | 10 | 25.0 |
| Long-term corticosteroid therapy | | |
| Yes | 5 | 12.5 |
| No | 35 | 87.5 |

ANC = absolute neutrophil count; CT = chemotherapy

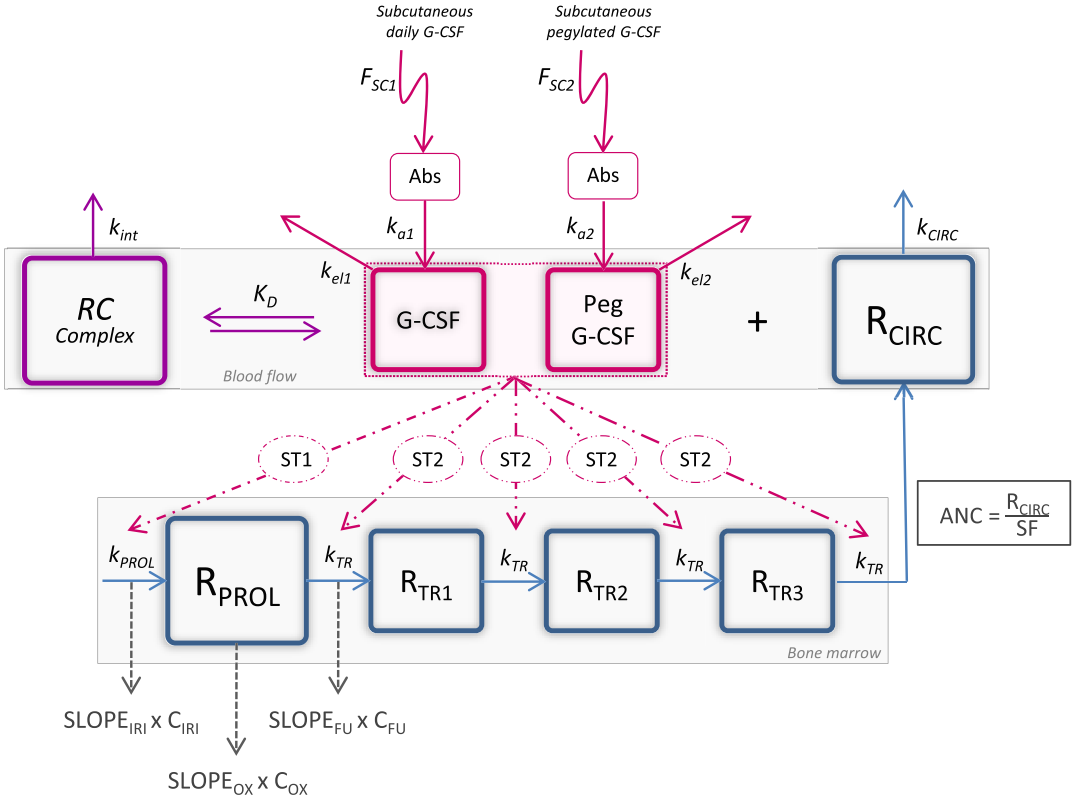


**FIGURE 1** Pharmacokinetic/pharmacodynamic model describing FOLFIRINOX myelotoxicity and effect of exogenous granulocyte colony-stimulating factor (G-CSF: pegylated or daily form) administration on ANC. Abs: absorption compartment; ANC: absolute neutrophils count; $C_X$: plasma drug X concentration; $F_{SC1/2}$: bioavailability of G-CSF/peg-G-CSF; G-CSF: free circulating G-CSF concentration resulting from exogenous G-CSF; $k_{a1/2}$: absorption rate constant of G-CSF/peg-G-CSF; $k_{CIRC}$: neutrophils elimination rate constant from systemic circulation; $K_D$: dissociation constant; $k_{el1/2}$: nonspecific elimination rate constant of G-CSF/peg-G-CSF; $k_{int}$: specific elimination rate constant of G-CSF/peg-G-CSF after binding to receptors and internalization; $k_{PROL}$: progenitors differentiation rate constant; $k_{TR}$: transit rate constant; peg-G-CSF: free circulating G-CSF concentration resulting from peg-G-CSF administration; $RC_{complex}$: bound G-CSF/peg-G-CSF (pharmacologically inactive); $R_{CIRC}$: circulating mature neutrophils receptors; $R_{PROL}$: precursor cells receptors; $R_{TR1-3}$: maturing granulocytes precursors receptors; SF: scaling factor representing cellular receptor density on ANC; $SLOPE_X$: sensitivity to drug X myelotoxicity; $ST_1$: process of stimulating neutrophils production; $ST_2$: process of stimulating neutrophils maturation

### 3.3 | Simulation-based evaluation of G-CSF and peg-G-CSF dosing schedule

Simulations were conducted to evaluate several G-CSF/peg-G-CSF dosing schedules and to propose an optimal schedule in biweekly-treated patients.

Out of the 1000 ANC time-course simulated without G-CSF, 25 fictitious individuals experienced severe neutropenia (grade III/IV) with a median ANC baseline of 3.15 $\times$ $10^9$/L and the remaining 975 individuals had a median ANC baseline of 5.65 $\times$ $10^9$/L.

To account for the high disparity between median ANC baseline values of the 2 groups, 3 ANC baseline cut-off were established to experiment G-CSF schedules: below the ANC baseline in subjects experiencing severe neutropenia (2.5 $\times$ $10^9$/L); above the ANC baseline in groups with moderate neutropenia or no neutropenia (6.5 $\times$ $10^9$/L); and between those 2 values (4.4 $\times$ $10^9$/L). For each ANC baseline, different G-CSF and peg-G-CSF dosing schedules were tested in 1000 virtual patients receiving 2 cycles of FOLFIRINOX. On both cycles, the percentage of patients experiencing all grade neutropenia or severe neutropenia with their median duration as well as the median nadir and number of patients who did not receive cycle 2 because of a low neutrophil count (<1 $\times$ $10^9$/L) were calculated. The results of model-based simulations are shown in Table 3. Plots of simulating neutrophils profiles for a moderate ANC baseline are provided in Figure S1.

## 4 | DISCUSSION

To date, no recommendation regarding prophylactic G-CSF administration in every-2-week chemotherapy, such as 5-FU-based chemotherapy, is defined. To manage FOLFIRINOX-induced neutropenia and optimize G-CSF dosing schedule, a thorough understanding of exposure/myelotoxicity relationship is necessary. We developed an exogenous G-CSF-integrated myelosuppression model able to describe ANC time-course in patients receiving FOLFIRINOX followed or not by G-CSF/peg-G-CSF administration, based on the original structure proposed by Friberg *et al.*[24]

**TABLE 2** Final parameters estimates and bootstraps results of the final PK/PD population model

| Parameters | Final estimates of model parameters | RSE (%) | Bootstraps results[a] | | Bootstrap median/final estimate ratio (%) |
|---|---|---|---|---|---|
| | | | Median | CI (90%)[b] | |
| *Fixed effects* | | | | | |
| $k_{PROL}$ (nM/h) | 0.0725 | 70.4 | 0.093 | 0.058–0.281 | 129 |
| $k_{TR}$ (h) | 0.028 | 7.75 | 0.029 | 0.023–0.035 | 103 |
| $k_{CIRC}$ (h) | 0.0714 | 37.5 | 0.061 | 0.053–0.085 | 85 |
| $STM_1$ | 1.06 | 46.1 | 1.51 | 0.91–4.78 | 142 |
| $STM_2$ | 5.18 | 41.4 | 7.92 | 4.85–36.08 | 152 |
| SF (nM/[× $10^9$/L]) | 0.181 | 63.6 | 0.272 | 0.170–0.905 | 150 |
| $SLOPE_{OX}$ (L/mg) | 4.08 | 61.3 | 2.86 | 0.99–5.61 | 70 |
| $SLOPE_{FU}$ (L/mg) | 8.6 | 31.8 | 7.5 | 6.7–10.5 | 88 |
| $SLOPE_{SN\text{-}38}$ (L/mg) | 432 | 13.1 | 413 | 402–858 | 96 |
| *Between-subject variability* | | | | | |
| $IIV_{KCIRC}$ (%) | 29 | 16.2 | 0.285 | 0.257–0.361 | 98 |
| $IIV_{STM1}$ (%) | 122 | 22.0 | 0.879 | 0.603–1.320 | 92 |
| $IIV_{STM2}$ (%) | 108 | 26.3 | 1.009 | 0.594–2.426 | 114 |
| $IIV_{SLOPEOX}$ (%) | 93 | 24.8 | 0.833 | 0.376–2.66 | 105 |
| *Exponential residual model error* | | | | | |
| $a_1$ | 0.422 | 4.4 | 0.419 | 0.384–0.467 | 99 |

[a]Based on 189 bootstrap simulations.
[b]5th and 95th percentiles of bootstrap parameter estimates.
CI: confidence interval; $k_{CIRC}$: neutrophils elimination rate constant from systemic circulation; $k_{PROL}$: progenitors proliferation rate constant; $k_{TR}$: transit rate constant; IIV: interindividual variability; RSE: Relative standard error expressed in %; SF: scaling factor representing cellular receptor density on absolute neutrophil count; $SLOPE_X$: sensitivity to drug X myelotoxicity; $STM_1$: stimulation of receptors production rate; $STM_2$: stimulation of transit rate between receptor compartments

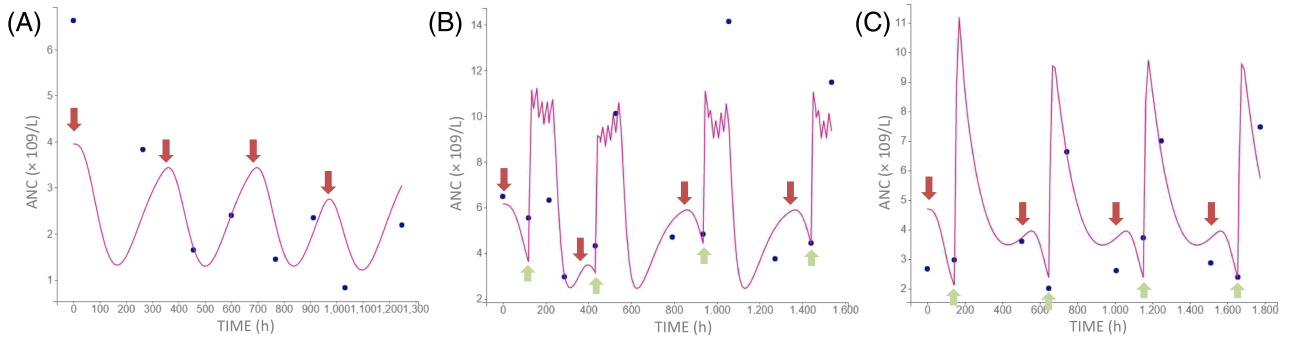


**FIGURE 2** Comparison plots between individual observations (dots) and individual predictions (solid lines) for: (A) a patient receiving FOFIRINOX regimen alone; (B) a patient receiving FOLFIRINOX regimen and granulocyte colony-stimulating factor (G-CSF) administration 48 hours after the end of chemotherapy during 5 days; and (C) a patient receiving FOLFIRINOX regimen and peg-G-CSF administration 48 hours after the end of chemotherapy. Red arrows represent dosing times for chemotherapy. Green arrows represent dosing time for G-CSF or peg-G-CSF. ANC: absolute neutrophil count

The Friberg model remains among the most frequently used semimechanistic myelosuppression models. In this PK/PD model, differentiation and maturation chain of precursor cells in the bone marrow, as well as circulating neutrophils pool, are mimicked by a 5-compartment model. To describe the effect of endogenous G-CSF, Friberg used an empirical feedback mechanism incorporated into the model to trigger return to ANC baseline, in particular after cytotoxic drug administration. However, this model was inapplicable for exogenous G-CSF effect. Therefore, numerous variant models were proposed to include this effect. Among them, Krzyzanski *et al.*[26] included a filgrastim receptor-binding model into the myelosuppression PK/PD model, to account for G-CSF receptor mediated clearance depending on the total neutrophil count. Similarly, the model proposed by Pastor *et al.* allows to predict the effect of pegylated and daily recombinant G-CSF after carboplatin administration.[27] Melhem *et al.* replaced the auto-proliferation loop of

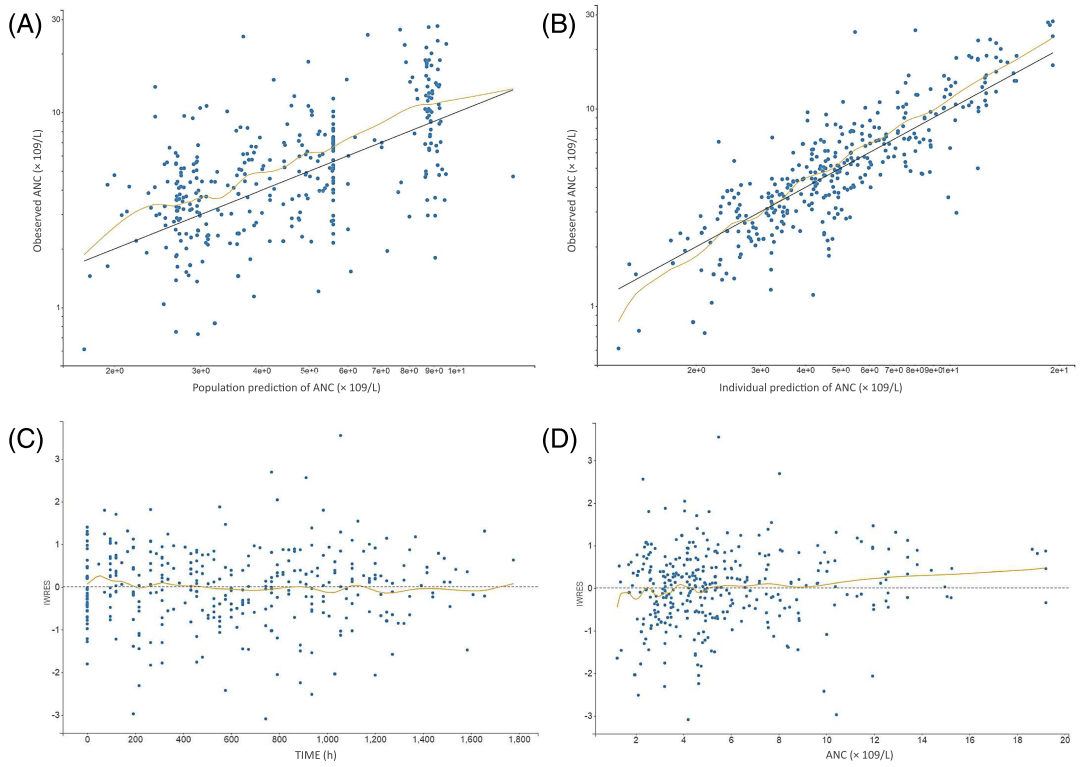


**FIGURE 3** Goodness-of-fit plots obtained with the final model. (A-B) Population and individual predict *vs* observed absolute neutrophil count on a log scale. (C) Individual weighted residuals (IWRES) *vs* time. (D) IWRES *vs* predicted concentrations. Dots represent individual data points. Solid lines represent reference lines (black) and linear regression lines (orange), striped lines represent theoretical mean (black) on individual data points

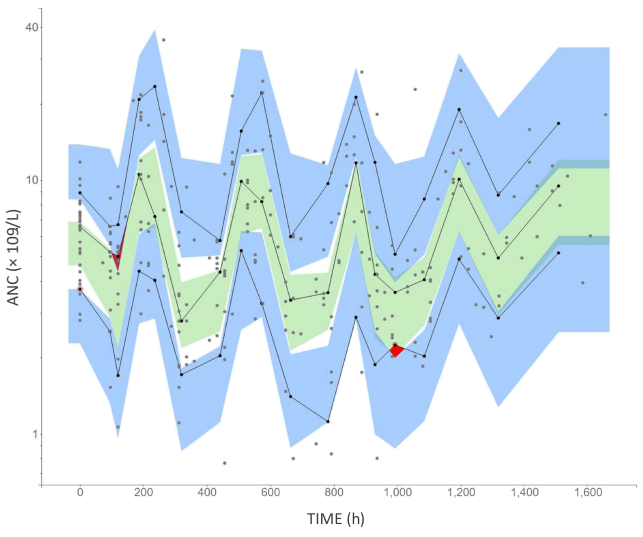


**FIGURE 4** Visual predictive checks of absolute neutrophil count for the final model based on 1000 simulations of study design on patients receiving daily granulocyte colony-stimulating factor after FOLFIRINOX regimen. Black dots represent the observed data. Red areas and circles represent deviation of the model predictions from mimicking the observed data. Solid lines refer to the median, 10$^{th}$ and 90$^{th}$ percentiles of observed data. Green area is the median 90% confidence interval and blue areas are 90% confidence interval for 10$^{th}$ and 90$^{th}$ percentiles of the model predictions. ANC: absolute neutrophil count

proliferative cells production, described in previous models, by a zero-order rate constant $k_p$ drove by the fraction of bound G-CSF receptors.[28] In this model, all compartments of ANC dynamic are represented as receptors and a scaling factor is used to translate G-CSF receptors concentration in the circulating mature-neutrophils compartment into ANC. For our analysis, we used the same method to design our myelosuppression model.

We have develop a PK/PD model in which cytotoxic dosing information for each patient was used to generate individual plasma concentration–time profiles using popPK parameters from previously published models for 5-FU,[31] oxaliplatin[32] and irinotecan.[33] To our knowledge, no publication has developed a myelosuppression model with a total of 3 cytotoxic treatments. Additive combination effect of 2 drugs have already been used in some studies,[38–42] but this addition of effect was not suitable in our case, as the model was unable to distinguish each individual drug effect. To overcome this difficulty, we have decided to implement each drug effect at distinct places of neutrophil differentiation and maturation chain. This atypical process, first used empirically, allowed to consider all the chemotherapy effects with a relative physiologically coherence: according to their pharmacology, SN-38 and oxaliplatin exert their cytotoxic action directly on the precursor cells' proliferation from progenitors' differentiation, while 5-FU cytostatic effect, described by an inhibition of DNA and RNA synthesis, is directed against maturation of precursor cells. Contrary to unsuccessful additive combination of multiple chemotherapy

**TABLE 3** Incidence and median duration of all grade and grade III/IV neutropenia for different granulocyte colony-stimulating factor (G-CSF) and pegylated (Peg)-G-CSF dosing schedules and for no G-CSF administration according high, moderate and low absolute neutrophil count (ANC) baseline simulated for 1000 virtual patients

| | | | For cycle 1 and cycle 2 | | | | | |
|---|---|---|---|---|---|---|---|---|
| ANC baseline ($\times 10^9$/L) | G-CSF schedule | G-CSF schedule duration (d) | All grade neutropenia incidence (%) | Severe neutropenia incidence (%) | All grade neutropenia median duration (d) | Severe neutropenia median duration (d) | Median nadir after D1 (d) | Number of patients who did not receive C2[a] |
| 6.5 | No G-CSF | / | 26.1 | 0.8 | 3.2 | 1.8 | 7,4 | 0 |
| 4.4 | No G-CSF | / | 64.8 | 9.9 | 5.1 | 2.9 | 7.1 | 0 |
| | Peg-G-CSF D4 | / | 38.1 | 7.6 | 1.2 | 0.6 | 4.0 | 3 |
| | Peg-G-CSF D5 | / | 54.4 | 13.9 | 1.3 | 1.0 | 5.0 | 3 |
| | Peg-G-CSF D6 | / | 67.4 | 21.1 | 1.9 | 1.6 | 6.0 | 11 |
| | Peg-G-CSF D7 | / | 69.8 | 18.9 | 2.7 | 2.2 | 7.0 | 11 |
| | G-CSF D4 | 1 | 70.0 | 16.8 | 4.1 | 2.0 | 7.9 | 0 |
| | G-CSF D4-D5 | 2 | 61.1 | 14.2 | 4.0 | 1.9 | 8.8 | 1 |
| | G-CSF D4-D6 | 3 | 56.4 | 9.6 | 3.7 | 2.1 | 9.8 | 0 |
| | G-CSF D4-D8 | 5 | 53.0 | 10.2 | 3.5 | 2.0 | 11.9 | 8 |
| | G-CSF D5-D7 | 3 | 62.5 | 10.8 | 3.7 | 1.6 | 10.8 | 1 |
| | G-CSF D5-D9 | 5 | 65.3 | 12.4 | 2.7 | 1.3 | 12.8 | 51 |
| | G-CSF D6-D10 | 5 | 77.8 | 21.6 | 2.5 | 1.0 | 13.8 | 70 |
| | G-CSF D7-D11 | 5 | 83.2 | 27.9 | 3.1 | 2.3 | 7.0 | 32 |
| 2.5 | No G-CSF | / | 97.0 | 54.8 | 10.1 | 4.1 | 6.9 | 5 |
| | Peg-G-CSF D4 | / | 83.6 | 31.9 | 3.7 | 1.0 | 4.0 | 16 |
| | Peg-G-CSF D5 | / | 92.2 | 51.3 | 3.4 | 1.1 | 5.0 | 13 |
| | Peg-G-CSF D6 | / | 95.1 | 58.9 | 3.8 | 1.8 | 6.0 | 13 |
| | Peg-G-CSF D7 | / | 97.0 | 63.8 | 4.5 | 2.6 | 6.9 | 18 |
| | G-CSF D4-D6 | 3 | 92.2 | 48.4 | 6.7 | 3.2 | 9.7 | 28 |
| | G-CSF D4-D8 | 5 | 90.9 | 45.4 | 5.8 | 2.7 | 11.7 | 197 |
| | G-CSF D5-D7 | 3 | 95.7 | 53.9 | 7.3 | 2.4 | 10.6 | 93 |
| | G-CSF D5-D9 | 5 | 95.8 | 60.4 | 5.3 | 1.9 | 12.6 | 334 |
| | G-CSF D6-D10 | 5 | 97.4 | 72.0 | 5.5 | 1.5 | 13.6 | 404 |
| | G-CSF D7-D11 | 5 | 99.3 | 76.3 | 6.2 | 2.6 | 7.0 | 282 |

[a]ANC baseline at C2 $<1 \times 10^9$/L.

effect, this unconventional method helped us to distinguish and estimate all of chemotherapies effects.

In the absence of G-CSF and peg-CSF PK data, some PD and all PK parameters referring to G-CSF were fixed to Melhem's publication values.[28] Parameters about effects of chemotherapies and ANC dynamic were estimated. In instance, the value of $k_{CIRC}$ has been evaluated to be equal to 0.071/h, corresponding to a calculated neutrophil half-life of 9.8 hours, in agreement with the reported mean neutrophil half-life of 7 hours.[26,37,41] Similarly, MTT determined in our model at the value of 6 days was reported in literature to be 4–6 days.[43,44] These 2 values are also similar to those determined by Melhem *et al*. whereas estimations of $k_{prol}$, $STM_2$ and $STM_1$ are slightly different from the Melhem model parameters. In our model, the maximum stimulatory effect on precursor maturation is higher than that of precursor production, which suggests that the use of exogenous G-CSF tends to favour the stimulation of neutrophils maturation rather than neutrophils proliferation. These results could explain why, during the administration of G-CSF, the concentration of neutrophils initially increase (faster transformation of precursors into neutrophils), and then quickly drop lower than before, due to lack of progenitors.

There are some limitations to this model. Indeed, in our analysis, only $SLOPE_{OX}$ IIV was estimated; this method allowed us to gather in a single parameter the IIV of the sensitivity to the myelotoxicity of the 3 concomitant chemotherapies, while avoiding over-parameterization of our model. Indeed, by considering the IIV on all SLOPE parameters, the model was not able to correctly estimate the parameters and no improvement of the OFV was observed. However, this process does not allow to independently determine variability related to each drug and, therefore, the potential covariates associated. All significant parameter–covariate relationships were tested but, despite high IIV, none of them significantly improved the structural model. Numerous case reports described the safe use of FOLFOX regimen in patients

with severe liver dysfunction,[45–47] whereas it was revealed that patients with poor liver function treated by irinotecan have a higher risk of presenting toxicities due to higher SN-38 AUC values.[48] These elements could partly explain why relationship between hepatic function parameters and sensitivity to myelotoxicity was discerned in early analysis. Another major constraint of the model is the absence of individual PK data on cytotoxics and G-CSF. The use of fixed popPK parameters for cytotoxics may lead to a rise of the IIV, because of the merging of PK and PD variability. Selecting published models with covariates could have made it possible to take into account part of the IIV. However, among all popPK models with covariates presented in Deyme's review,[49] none of them were suitable, because of different population than in our study (i.e. paediatric patients, kidney/hepatic impaired adults) or unavailable covariates. Other relevant models with available covariates were considered but they did not allow to significantly reduce AIC and BIC or decrease IIV (data not shown).

External model validation by data splitting was disregarded because the data splitting would have decreased the already limited amount of information. The absence of significant covariates and difficulty to precisely estimate few parameters (RSE > 50%) may be due to the limited number of patients enrolled in this study. Overall, the present PK/PD model successfully describes and predicts the neutrophil time course in our population.

In accordance with international guidelines, G-CSF administration is recommended as primary prophylaxis in patients who have a high risk of FN. Among risk factors for patient-associated FN, age >65 years, female sex, comorbidities (renal and liver dysfunction), prior chemotherapy recent corticosteroid use were frequently reported.[8,50] Importantly, none of the analysed demographic, pharmacological or biological covariates tested had a significant impact on neutropenia-induced sensitivity or neutrophil maturation related parameters. Despite high IIV on $STM_1$, $STM_2$ and $SLOPE_{OX}$, the absence of obvious covariates indicates that risk factors currently described have no or limited impact on FOLFIRINOX-induced neutropenia in our population. Additionally, it suggests that unknown factors are likely to explain these strong disparities between patients. As no supplementary information on chemotherapies and patient characteristics was available, this could not be further investigated.

Low ANC baseline has also been correlated with the risk of developing FN.[51,52] For instance, in Jenkin's risk model, pretreatment ANC ≤$3.1 \times 10^9$/L was strongly associated to the risk of neutropenic events or FN. Independently of previous chemotherapy lines, a similar result was observed in our model: it was calculated that patients experiencing severe neutropenia had a median ANC baseline of $3.15 \times 10^9$/L, while patients who presented grade 0/I/II had a median ANC baseline of $5.65 \times 10^{9/}$L. Furthermore, mean ANC baseline value estimated by our popPK/PD model was approximately the same as the population median observed ($6.03 \times 10^9$/L). This high value could explain why only 4 patients (1 without G-CSF and patients with G-CSF) from the whole population experienced severe neutropenia. Since these data confirmed a higher risk of neutropenia in patients with low initial neutrophil count, ANC baseline level has been accordingly a fundamental and decisive value of simulations for the assessment of G-CSF schedules.

Simulations were performed to explore the impact of different G-CSF formulations on neutrophil time-course during chemotherapy and provide guidance for G-CSF administration following FOLFIRINOX regimen. Due to large heterogeneity in start and duration of observed G-CSF administration, we simulated numerous dosing schedules similar to those realized in clinical practice. Using the PK/PD model built beforehand, G-CSF schedules in patients with high, moderate and low ANC baseline were investigated. As expected, in patients with a high initial neutrophils count, because of a limited risk of severe neutropenia associated to short duration, G-CSF administration does not seem necessary. For moderate and low ANC baseline, peg-G-CSF administration 1 or 2 days after the end of 5-FU infusion seems to be the optimal schedule to reduce all grades neutropenia and median duration. Thus, long-acting G-CSF should be more efficient than several repeated administrations of daily formulation, in patients receiving FOLFIRINOX. These findings are supported by the literature reporting lower incidence of CIN, FN, hospitalisation, antibiotic use and adverse events with pegfilgrastim compared to filgrastim.[10,27,53–56] Indeed, although some studies suggest a similar efficacy and safety profile with pegfilgrastim and 11 days of filgrastim[57,58] in clinical practice, duration of filgrastim treatment is routinely shorter than 11 days, in particular in every-2-weeks chemotherapy. By contrast, 3 days of daily G-CSF administration starting 24 hours after the end of chemotherapy can also be a good alternative schedule if moderate ANC is observed at baseline (cf. Table 3). We observed that 3 consecutive days of G-CSF show better results than 5 days. This observation can be partly explained by the rapid maturation of granulocytes in the bone marrow after G-CSF administration, which often leads to a transient depletion of the precursor cells pool, characterized by a neutropenia rebound and regenerative delay. This process accounts for the increased number of simulated subjects who did not receive a second cycle (ANC baseline at C2 < $1 \times 10^9$/L) when G-CSF was administered beyond 48 hours after the end of chemotherapy, due to a median nadir delayed depending on the day of injection start. As already highlighted by Schmitt *et al.*,[59] the critical finding of these model-based simulations was that late G-CSF and peg-G-CSF administration (3 and 4 days after end of chemotherapy) is worse compared to no G-CSF administration. These results demonstrate that, in bimonthly chemotherapy such as the FOLFIRINOX regimen, peg-G-CSF administration 24–48 hours after the end of 46-hour continuous infusion of 5-FU appears to be the optimal G-CSF dosing schedule to restrain incidence and duration of CIN. However, considering the strong unexplained IIV, these findings need to be confirmed in a future clinical trial.

In conclusion, through this PK/PD model, we were able to adequately describe the time course of ANC in FOLFIRINOX-treated cancer patients, as well as the effect of G-CSF and peg-G-CSF on dynamics of neutrophil proliferation and maturation. The model presented was useful in clarifying the neutrophils stimulating effect of different G-CSF formulations and highlighting how an optimal dosing schedule after the FOLFIRINOX regimen could be selected. Beyond

standard risk factors of vulnerability to neutropenia, it appears as fundamental to consider ANC baseline at each cycle as a potential risk factor of neutropenia. Model-based simulations suggest that pegfilgrastim should probably be preferred to daily formulation because of its ability to reduce the incidence and duration of neutropenia. We also underlined the potential negative effect of late G-CSF administration or inappropriate treatment duration.

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## COMPETING INTERESTS

There are no competing interests to declare.

## CONTRIBUTORS

Study conception and design: F.G., A.S. Acquisition of data: J.V., F.G., L.B.L. Analysis and interpretation of data: P.M., J.P., A.S. Drafting of manuscript: P.M., A.S. Critical revision: P.M., F.G., L.B.L., A.S. Final approval: P.M., J.P., J.V., F.G., L.B.L., A.S.

## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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## SUPPORTING INFORMATION

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