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RESEARCH PAPER

Model-Based Approach to Early Predict Prolonged High Grade Neutropenia in Carboplatin-Treated Patients and Guide G-CSF Prophylactic Treatment

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ABSTRACT

Purpose Neutropenia is a major dose-limiting side effect of chemotherapy and is closely related to febrile neutropenia which mainly occurs during the first cycle. Our objectives were to establish model-based decision rules from early absolute neutrophil counts (ANC) to anticipate prolonged high grade neutropenia at cycle 1 and to prevent it through delayed granulocyte colony stimulating factor (G-CSF) administration in carboplatin-treated patients.

Methods The decision rules were built from Monte Carlo simulations performed with a previously published semi-mechanistic model describing ANC time-course in carboplatin-treated patients with or without concomitant G-CSF therapy.

Results ANC measured at day 0 (D0, baseline), D4 and D5 were good predictors of prolonged high grade neutropenia at cycle 1. Pegfilgrastim administration on D5 was as effective as the conventional pegfilgrastim administration on D1 but none avoided prolonged high grade neutropenia in all patients. Additional decision rules were thus derived, using the same ANC combination, to identify patients for whom G-CSF was beneficial. All decision rules showed good performances (sensitivity/specificity).

Conclusion We propose an innovative approach to guide oncologist in their clinical practice. The next step is to perform prospective studies to implement, validate and possibly refine the proposed decision rules.

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KEY WORDS chemotherapy · decision rule · G-CSF · neutropenia · semi-mechanistic model

ABBREVIATIONS

ANC	Absolute neutrophils counts
G-CSF	Granulocyte colony-stimulating factor
ROC	Receiver-operating characteristic

INTRODUCTION

Neutropenia is one of the most common dose-limiting side effects of cytotoxic drugs, including carboplatin. Because of the risk of infection, chemotherapy-induced neutropenia is a major concern and requires dose adjustments or delays in anticancer drug administration which may compromise clinical outcome, especially in curative regimens (1). Febrile neutropenia is defined as fever or clinical signs of sepsis associated with high grade neutropenia corresponding to absolute neutrophil count (ANC) below 1×10^9/L, i.e., grades 3 and 4 (2,3). The occurrence of febrile neutropenia is associated with the severity and duration of neutropenia, particularly high grade neutropenia lasting for more than 3 days (2,4,5). More precisely, the incidence of febrile neutropenia is close to 20% if a severe neutropenia lasts 3 days, close to 40% if a severe neutropenia lasts more than 4 days and odds ratio for febrile neutropenia was 2.28 per additional day of severe neutropenia (6,7). Thus, with regards to adverse events of anticancer drugs, one objective of oncologists is to avoid prolonged high grade neutropenia to prevent febrile neutropenia.

In order to reduce the severity and duration of neutropenia, granulocyte colony-stimulating factor (G-CSF) is frequently administered to patients considered to be at risk (8–11). Exogenous G-CSF reproduces the physiological effect of its endogenous counterpart, that is to say it increases the proliferation of granulocytes progenitors, reduces their

maturation time and stimulates their release from the bone marrow storage pool (12,13). The actual benefit of the systematic use of G-CSF remains, however, controversial because of its cost and potential side effects (bone pain, headache, secondary malignancies,…(9)). To target the patients who would benefit from G-CSF treatment, it is recommended to assess the risk of febrile neutropenia before each chemotherapeutic agent administration. As recently stated by the European Organization for Research and Treatment of Cancer (EORTC) (3,14,15), this risk depends on tumor type (breast, lung, colorectal, lymphoma, and ovarian), chemotherapy regimen and patient-related risk factors such as elderly age (≥65 years), female gender, advanced-disease stage, previous episode of febrile neutropenia, presence of comorbidities and poor performance/nutritional status. Oncologists have to evaluate the risk of febrile neutropenia at the beginning of each cycle, taking all these factors into consideration. When the overall risk is above 20%, prophylactic G-CSF administration is then recommended (Fig. 1) (3,9,14).

In order to refine the evaluation of the risk of febrile neutropenia and/or high grade neutropenia, several model-based approaches have been proposed. Particularly, semi-mechanistic myelosuppression models have been developed to describe ANC-time profiles in cancer patients under various chemotherapy regimens (see (16–18) for reviews). Most of these models are population pharmacokinetic/pharmacodynamic (PK/PD) models as they aim to describe the variability in the disposition of anticancer drugs in the body as well as the variability in the relationship between the circulating drug concentration and the myelosuppressive effect. A popular population PK/PD model is the Friberg model (19). The advantage of such models is that they capture the whole time course of ANC, account for between-patient variability and provide individual predictions despite relatively sparse ANC measurements per patient. For docetaxel, it has been shown that model-based individual predictions were superior predictors over descriptive values (i.e. nadir, neutropenia duration) for the probability of experiencing febrile neutropenia (20). Individual predictions derived from ANC at early cycles have also been used to guide dose adaptation in chemotherapy in order to prevent high grade neutropenia in subsequent cycles (21,22). All these methods require to run a professional software (e.g. NONMEM) or to implement model-related differential equations in an Excel file following Wallin *et al.* (21), which may restrict the use of such approaches in clinical practice.

In the present work, we propose to derive simple model-based decision rules that predict prolonged high grade neutropenia and guide G-CSF prophylactic treatment in carboplatin-treated patients. These decision rules shall only be based on a combination of sparse ANC without requiring complex manipulations of the data to compute individual predictions. Furthermore, we focus on the first treatment cycle since most episodes of febrile neutropenia occur at that time (20,23,24). Our goal was thus to propose a way to identify, from early ANC, patients who have a high risk to experience prolonged high grade neutropenia at cycle 1 and who would benefit from a prophylactic administration of G-CSF. To achieve this objective, we performed Monte Carlo simulations using a previously published semi-mechanistic model for ANC, integrating the effect of endogenous and exogenous G-CSF (25). This model was developed from 375 patients receiving carboplatin as mono- or poly-chemotherapy over 2 cycles, among whom 47 received G-CSF as a once-per-cycle formulation (pegfilgrastim) or as a daily formulation (filgrastim, lenograstim). Conventionally, G-CSF is given on

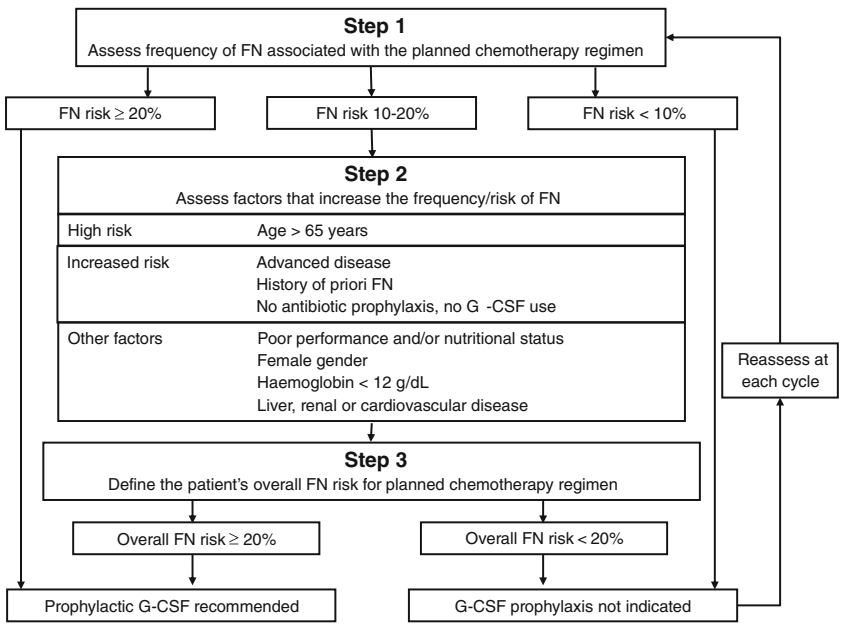

Fig. 1 2010 EORTC algorithm for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors. Permission to publish has been accepted by Elsevier and this figure was taken from the article of Aapro et al. (ref [30]).

the first day following anticancer drug administration, i.e., on day 1 (D1). With the proposed approach, we considered a delayed G-CSF (pegfilgrastim) administration at D5 of cycle 1. We show through Monte Carlo simulations that these two dosing times are equally effective in limiting prolonged high grade neutropenia in carboplatin-treated patients.

MATERIAL AND METHODS

Semi-mechanistic Myelosuppression Model Used for Monte Carlo Simulations

In a previous work (25), we developed a population pharmacokinetic/ pharmacodynamic model that described neutrophil-time course in 375 cancer patients with various malignant tumors, receiving carboplatin as part of established regimens as monochemotherapy or in combination with different other cytotoxic drugs. Among the 375 patients, 47 had G-CSF administration given subcutaneously as a daily formulation ($N=31$; filgrastim (Neupogen®) or lenograstim (Granocyte®) at 5 μg/kg/day) or a pegylated once-per cycle formulation ($N=17$; pegfilgrastim (Neulasta®) at 6 mg/kg). Details about G-CSF administration schedule and the reasons of G-CSF administration in those particular patients are given in the previous published article (25). Carboplatin was given as a single intravenous infusion over 30 or 60 min at the beginning of each cycle, with a theoretical intercycle period of 21 days. Four blood samples were taken to measure carboplatin-ultrafiltrable plasma concentrations during the first two cycles: before the start of carboplatin infusion, 5 min before the end of the infusion, and at 1 and 4 h after the end of the infusion. Cell blood counts were scheduled before chemotherapy and then weekly during the intercycle period. In total, 2991 ANC values were available from the first two cycles to build the model. The protocol was approved by the ethical committee of Toulouse, and informed written consent was obtained from each patient. The model was developed in NONMEM software version 7.2 and was validated using appropriate techniques (25).

A schematic representation of the model is displayed in Fig. 2. The model comprises two parts. The first part mimics the granulopoiesis and consists of five compartments: one compartment representing proliferative cells in the bone marrow, three maturation compartments, and one compartment for circulating neutrophils in blood, as in the conventional Friberg's model (19). The rate constant for the physiological elimination of circulating neutrophils from blood (k_{circ}) was assumed to be equal to the rate constant for maturation (k) under steady-state conditions (i.e. at baseline). Under no steady-state conditions (i.e. following chemotherapy and possible co-administration(s) of exogenous G-CSF), k was not anymore a constant but varied over time as the result of the effect of G-CSF on the maturation rate of precursors in the bone marrow. The mean maturation time (or mean transit time *MTT*) was defined as $(n+1)/k$ where n was the number of maturation compartments. The carboplatin ultrafiltrable plasma concentration was assumed to induce cell loss from the proliferative cell compartment by increasing apoptosis. Carboplatin effect was proportional to carboplatin plasma concentration, the *Slope* being the coefficient of proportionality.

The second part of our model describes the pharmacokinetics of endogenous and exogenous G-CSF and its effects on the proliferation and maturation of progenitors in the bone marrow. The free G-CSF concentration in blood was described by a one-compartment model with zero-order input k_{GCSF} to mimic the endogenous production of G-CSF. Free circulating G-CSF could be eliminated by two mechanisms: a linear and a non-linear elimination. More precisely, free G-CSF could either be eliminated by the kidneys (with first-order rate constant k_{el}) or could bind to receptors R present on circulating neutrophils (with dissociation constant K_D), followed by an internalization and degradation (rate constant k_{int}). In our clinical studies, patients not only received filgrastim but could also received lenograstim or pegfilgrastim. Identical pharmacokinetic parameters were assumed for filgrastim and lenograstim which are both recombinant forms of endogenous G-CSF and immediate-release daily formulations. Note that filgrastim and lenograstim show the same clinical efficacy at the same dosage (3). Concerning pegfilgrastim, the pegylation results in major differences in the pharmacokinetics with a different absorption rate constant, a different apparent volume of distribution (VD_a) and, more importantly, a much reduced rate of renal elimination (26–28). To account for these differences in pharmacokinetics, different sets of pharmacokinetic parameters were used for pegfilgrastim and filgrastim/lenograstim with separate absorption and central compartments. In both cases, values of k_a, VD_a and k_{el} were taken from the literature. Concerning filgrastim/lenograstim, they were denoted k_a1, VD_a1 and $k_{el}1$ and fixed to the previously published values in Krzyzanski *et al.* (29). In the case of pegfilgrastim, they were denoted k_a2, VD_a2 and $k_{el}2$. The values of k_a2 and VD_a2 were taken from Roskos *et al.* (27) while $k_{el}2$ was fixed to 20% of $k_{el}1$ based on the modeling work of Scholz *et al.* (28) in man. As in physiological conditions, G-CSF could stimulate stem cells proliferation and accelerate maturation time in the bone marrow. These effects were assumed to be driven by the free circulating G-CSF concentration using two standard E_{max} models, each defined by two parameters: a maximal effect ($E_{max}1$ and $E_{max}2$, respectively) and a potency parameter ($EC_{50}1$ and $EC_{50}2$, respectively). All modeling details and differential equations are provided in the Appendix.

Model parameters are given in Table I. Inter-individual variability was set on baseline ANC (*Base*), mean maturation

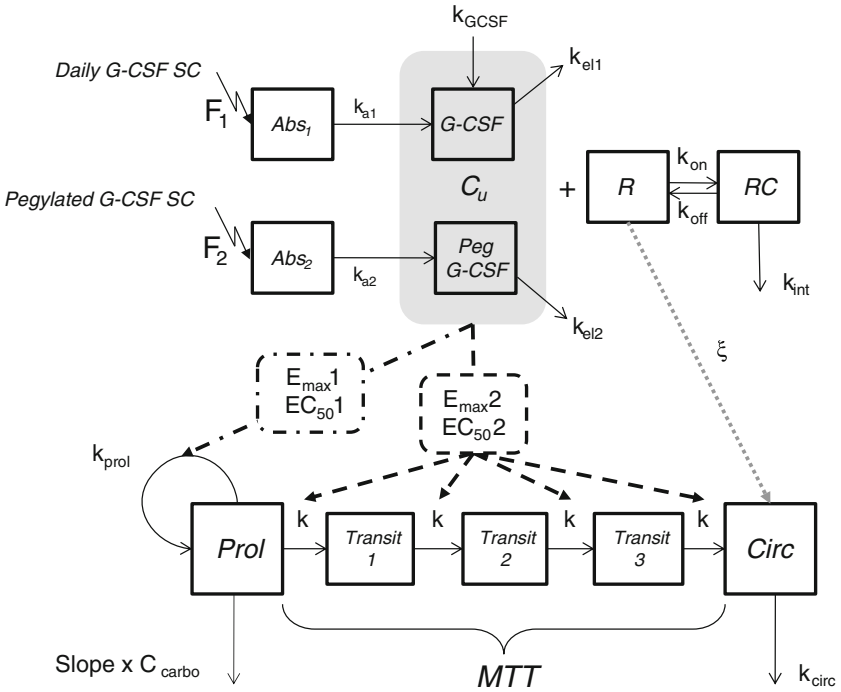

Fig. 2 PK/PD model describing the neutropenic effect of carboplatin with G-CSF-based feedback mechanism. The effect of G-CSF (pegylated or non-pegylated form) on proliferation and maturation processes in bone marrow were assumed to be driven by the free circulating G-CSF concentration. Standard E_{max} models were used for that purpose (see Appendix for more details). The G-CSF receptor complex RC in blood was assumed to be pharmacologically inactive. *Prol* proliferative cells in bone marrow; *Transit* maturating granulocyte precursors in bone marrow; *Circ* circulating mature neutrophils; *MTT* mean transit time for maturing precursors in bone marrow; *Slope* sensitivity to carboplatin myelotoxicity; C_{carbo} ultrafiltrable plasma concentration of carboplatin; k_{prol} proliferation rate constant; *k* transit rate constant; k_{circ} rate constant of elimination of neutrophils from the systemic circulation; *SC* subcutaneous; Abs_1 absorption compartment for filgrastim/lenograstim; Abs_2 absorption compartment for pegfilgrastim; *F1 (F2)* bioavailaility of filgrastim/lenograstim(pegfilgrastim); C_u free circulating concentration controlling G-CSF effects on bone marrow, calculated as the sum of non-pegylated and pegylated G-CSF free circulating (serum) concentrations; *R* G-CSF receptors on circulating neutrophils; ξ proportionality constant for the amount of G-CSF receptors per cell; *G-CSF* free circulating G-CSF concentration resulting from endogenous production or from an administration of filgrastim/lenograstim; *peg-GCSF* free circulating G-CSF concentration resulting from an administration of pegfilgrastim; *RC* bound non-pegylated and pegylated G-CSF assumed here to be pharmacologicaly inactive; k_{on}/k_{off} on/off-rate constants with dissociation constant $K_D = k_{off}/k_{on}$; k_a1 *(2)* absorption rate constant for filgrastim/lenograstim (pegfilgrastim); k_{GCSF} zero-order rate constant of endogenous G-CSF production; $k_{el}1$ rate constant for the linear, non-specific elimination of endogenous G-CSF and filgrastim/lenograstim; $k_{el}2$ rate constant for the linear, non-specific elimination of pegfilgrastim; k_{int} rate constant for non-pegylated or pegylated G-CSF elimination after binding to receptors and internalization; $E_{max}1$ *($E_{max}2$)* maximal effect of non-pegylated or pegylated G-CSF on progenitor proliferation (precursor maturation); $EC_{50}1$ *($EC_{50}2$)* free non-pegylated or pegylated G-CSF concentration eliciting 50% of the maximal effect.

time (*MTT*), and carboplatin myelotoxicity (*Slope*), assuming a log-normal distribution. Inter-occasion variability (IOV) was set on *Slope*. Corticosteroid multiple administration at the start of the cycle increased *Base* by 25%. An exponential error model was used to model the residual variability, including ANC measurement error and model departure from the observed data.

Monte Carlo Simulation and Derived Decision Rules

Our objectives were to build decision rules from early ANC measured between D0 (baseline) and D5 in order to detect patients at risk for prolonged high grade neutropenia, and to evaluate the benefit of a delayed G-CSF administration on D5 (single subcutaneous injection of 6 mg of pegfilgrastim) to prevent this event. Note that these decision rules were not built sequentially but independently from each other. More precisely, the second decision rule aims to identify directly the patients who shall experienced high grade neutropenia *and* shall benefit from a prophylactic G-CSF administration. A patient was considered to have prolonged high grade neutropenia when the ANC was lower than 1×10^9/L (grade 3 to 4) for at least 3 consecutive days. Prolonged *severe* neutropenia was also investigated, corresponding to ANC below 0.5×10^9/L (grade 4 only) for at least 3 days.

We proceeded in a stepwise manner. The first step was to confirm the relevance of a delayed G-CSF administration on D5 compared to the conventional day 1 administration with respect to prolonged high grade/severe neutropenia. The second step was to find the best combination of ANC between D0 and D5 predicting the occurrence of prolonged high grade/severe neutropenia during the first treatment cycle. The third and final step was to identify patients for whom G-CSF administration on day 5 prevented this event. Indeed,

Table I Semi-mechanistic Myelosuppression Model Used for Simulations

	Model parameters	Value (IIV)
PK-PD estimated parameters	**Base** $= \theta_1 \times (1 - \text{CORT}) + \theta_2 \times \text{CORT}$ CORT = 0 or 1	$\theta_1 = 4.88 \times 10^9$/L (30%) $\theta_2 = 6.13 \times 10^9$/L
	$\theta_{MTT_0} = \theta_3$	$\theta_3 = 185$ h (21%)
	Slope $= \theta_5$	$\theta_5 = 0.0161$ L/(mg.h) (22%) IOV = 34%
	$\mathbf{E_{max}2} = \theta_6$	$\theta_6 = 3.73$
	$\mathbf{EC_{50}1} = \theta_7$	$\theta_7 = 0.0763$ ng/mL
	$\mathbf{EC_{50}2} = \theta_8$	$\theta_8 = 0.402$ ng/mL
	Residual variability	52.1%
PK parameters of G-CSF (fixed as in [25–27])	$\mathbf{E_{max}1}$	34.7
	$\mathbf{k_a1}$	0.0228 h^{-1}
	$\mathbf{k_a2}$	0.651 h^{-1}
	$\mathbf{VD_a1}$	5.07 L
	$\mathbf{VD_a2}$	4.02 L
	$\mathbf{k_{int}}$	0.105 h^{-1}
	$\mathbf{k_{el}1}$	0.152 h^{-1}
	$\mathbf{k_{el}2}$	$0.2 \times k_{el}1$ h^{-1}
	$\mathbf{K_D}$	1.44 ng/mL
	$\boldsymbol{\xi}$	0.181 fg/cell

IIV interindividual variability; *IOV* intraindividual (interoccasion) variability; *Base* baseline level of absolute neutrophil count; *CORT* = 1 means that the patients received multiple administration of corticosteroids (>4 days) (*CORT* = 0 otherwise); θ_{MTT_0} population parameter for mean transit time at baseline (MTT_0) such that $MTT_0 = \theta_{MTT_0}/H_{20}$ where H_{20} is the Hill function for the effect of free G-CSF on maturation rate (see Appendix for more details); *Slope* sensitivity to carboplatin cytotoxicity; $E_{max}1$ (2) maximal effect of G-CSF on proliferation (maturation); $EC_{50}1$ (2) free G-CSF concentration eliciting 50% of the maximal effect on proliferation (maturation); k_a1 (2) absorption rate constant for the daily (pegylated) formulation; VD_a1 (2) apparent volume of distribution for the daily (pegylated) formulation; k_{int} rate constant for non-pegylated and pegylated G-CSF elimination after binding to receptors and internalization; $k_{el}1$ rate constant for the linear, non-specific elimination of endogenous G-CSF and filgrastim/lenograstim; $k_{el}2$ rate constant for the linear, non-specific elimination of pegfilgrastim; K_D dissociation constant of RC complex; ξ proportionality constant for the amount of G-CSF receptors per cell

as will be shown in the results section and will be further discussed, G-CSF administration did not avoid neutropenia in all patients.

To achieve these objectives, Monte Carlo simulation studies were performed with the model for the first treatment cycle, taking into account between-subject variability and measurement error (residual unexplained variability). A large number of patients were simulated using the carboplatin dosing regimen (dose, infusion rate), the covariate "multiple corticosteroid administration" and the pharmacokinetic parameters of the 375 patients of the clinical study at cycle 1. More precisely, 28 replications of the study design were simulated using the PK profiles of the 375 patients of the clinical study (using their empirical Bayes estimates) in order to generate 10500 ANC profiles. While inter-individual variability was simulated in the ANC model, the model included no interindividual variability in G-CSF PK parameters. For patients receiving multiple corticosteroid administration (32% of the patients), the first dose of corticosteroids was given before ANC measurement at baseline. Three different scenarios were then tested for each simulated patient: scenario (1), no G-CSF therapy; scenario (2), pegfilgrastim administration on D1 (i.e. on the day after carboplatin administration); scenario (3), pegfilgrastim administration on D5. For each patient and each scenario, ANC were simulated every 24 h over 21 days corresponding to one theoretical cycle. Scenarios (2) and (3) were used to compare dosing times of pegfilgrastim in terms of efficacy in the prevention of prolonged high grade neutropenia, using individual predictions. Based on scenario (1), logistic regression analyses were performed to identify, from the first ever ANC, the best predictors of prolonged high grade/severe neutropenia when no G-CSF was given. Grade 3–4 and grade 4 neutropenia were successively addressed and decision rules were derived to minimize the global risk (sensibility equal to specificity). Finally, the same approach was applied based on scenarios (1) and (3) to identify patients from whom G-CSF would be beneficial, i.e., patients who would experience neutropenia in the absence of G-CSF treatment and none when G-CSF is given. Again, decision rules were derived to minimize the global risk (sensibility equal to specificity).

RESULTS

Relevance of Pegfilgrastim Administration on Day 5 With Respect to Prolonged High Grade Neutropenia at Cycle 1

The percentage of patients experiencing prolonged grade 3–4 neutropenia during the first treatment cycle was 11.4% when pegfilgrastim was administered on D1 and 9.6% when pegfilgrastim was administered on D5. This percentage was increased to 18.2% when no G-CSF was administered. Regarding severe neutropenia, the percentage of patients experiencing prolonged grade 4 neutropenia was 3.5% when pegfilgrastim was administered on D1 and 3.0% when pegfilgrastim was administered on D5 *versus* 5.8% in the absence of G-CSF treatment. To summarize, the simulation studies showed that pegfilgrastim administration on D5 was as effective as the conventional administration on D1. They also showed that pegfilgrastim administration did not avoid

neutropenia in all the patients, whatever the time of administration (D1 or D5).

Decision Rules to Identify At-Risk Patients for Neutropenia at Cycle 1

From the logistic regression analyses, the best predictors to detect prolonged high grade (grade 3–4) and prolonged severe (grade 4) neutropenia were the ANC on D0 (ANC_0), D4 (ANC_4) and D5 (ANC_5). Corresponding receiver-operating characteristic (ROC) curves are shown in Fig. 3. The area under the ROC curve was 87.5% for the prediction of prolonged high grade neutropenia and 89.2% for the prediction of prolonged severe neutropenia.

Decision rules were derived from these logistic regression equations to achieve similar values for sensitivity and specificity. These decision rules are displayed in Table II: the equations provided are based on the natural logarithm of ANC_0, ANC_4 and ANC_5. The patient is considered at risk of prolonged high grade or severe neutropenia when the equation gives a positive result (i.e. ≥ 0). Sensitivity/specificity values were 79%/79% for prolonged high grade neutropenia, and 81%/81% for prolonged severe neutropenia. When only ANC_0 and ANC_5 were used, sensitivity/specificity values fell to 75%/75% for prolonged high grade neutropenia, and 79%/80% for prolonged severe neutropenia.

Decision Rules to Identify Patients for Whom G-CSF Administration on Day 5 Would Prevent Prolonged High Grade Neutropenia

As shown previously, G-CSF did not prevent prolonged high grade in all patients. Given the cost and side effects of G-CSF treatment (9), it thus appeared important to target patients for whom G-CSF administration would be beneficial, i.e. patients who would experience prolonged high grade/severe neutropenia in the absence of G-CSF treatment and none when G-CSF is given. Logistic regression analyses were performed on the 10500 simulated patients with the same predictors as previously (ANC_0, ANC_4 and ANC_5). The corresponding ROC curves are shown in Fig. 4, with an area under the curve of 87.4% for grade 3–4 and 89.2% for grade 4 only.

As before, decision rules were derived from these logistic regression equations to achieve similar values for sensitivity and specificity. These decision rules are given in Table III: the equations provided are based on the natural logarithm of ANC_0, ANC_4 and ANC_5. The patient is considered to benefit from pegfilgrastim administration on day 5 when the equation gives a positive result (i.e. ≥ 0). As already stated, this equation stand by itself and does not require the result of the preceding decision rule. Sensitivity/specificity values were 73%/73% in the case of prolonged high grade neutropenia and 79%/79% in the case of prolonged severe neutropenia. When only ANC0 and ANC5 were used, sensitivity/specificity values fell to 69%/70% in the case of prolonged high grade neutropenia and 76%/76% for prolonged severe neutropenia.

DISCUSSION

Using a previously published population PK/PD model (25), we have derived decision rules 1) to predict prolonged high grade neutropenia for cycle 1 using early ANC in patients and 2) to guide potential G-CSF administration on D5 to prevent this event. The decision rules were established independently of each other in patients treated with carboplatin as part of established regimens as monochemotherapy or in combination with different other cytotoxic drugs. They rely on a small number of early ANC measured on D0, D4 and D5. All decision rules achieved very good performances as evaluated by the percentage of true positives (sensibility) and true

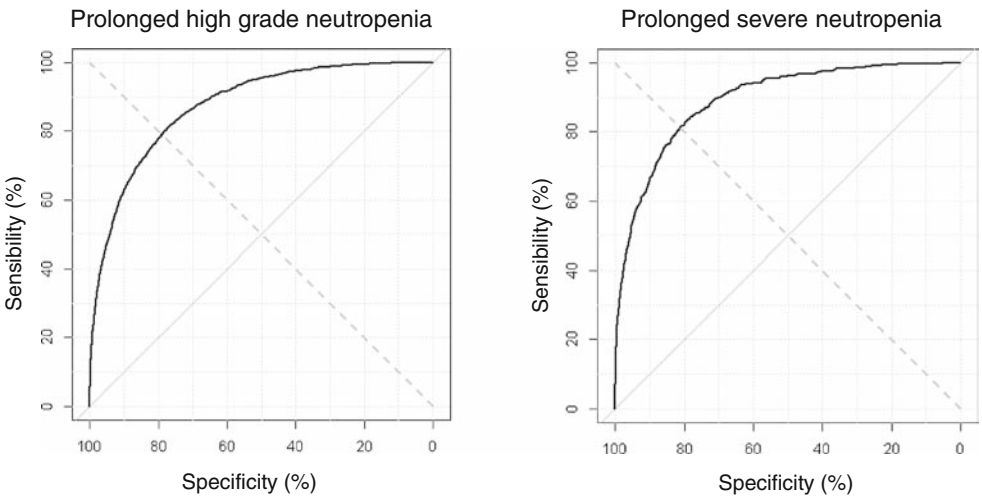

Fig. 3 Receiver-operating characteristic (ROC) curves for the decision rules to identify at-risk patients for prolonged (at least 3 days) neutropenia at cycle 1. *Left*: ROC curve for the prediction of high grade neutropenia, i.e., grade 3 and 4; *right*: ROC curve for the prediction of severe neutropenia, i.e., grade 4. In all cases, the best predictors were ANC on day 0 (ANC_0), day 4 (ANC_4) and day 5 (ANC_5).

Table II Decision Rules to Identify At-Risk Patients for Neutropenia in the First Treatment Cycle. Prolonged Neutropenia Means a Neutropenia Lasting for 3 Days or More. The Patient is Considered at Risk When the Decision Rule Equation Gives a Positive Value

Prediction of patients at cycle 1 with	Decision rule equations with 2 or 3 early ANCs	Se/Sp
Prolonged grade 3–4 neutropenia	$1.035 - 0.052 \times \log(ANC_0) - 2.004 \times \log(ANC_5) > 0$	0.75/0.75
	$5.139 + 0.066 \times \log(ANC_0) - 1.363 \times \log(ANC_4) - 1.873 \times \log(ANC_5) > 0$	0.79/0.79
Prolonged grade 4 neutropenia	$-0.239 + 0.053 \times \log(ANC_0) - 2.283 \times \log(ANC_5) > 0$	0.79/0.80
	$4.123 + 0.275 \times \log(ANC_0) - 1.188 \times \log(ANC_4) - 1.979 \times \log(ANC_5) > 0$	0.81/0.81

Se sensitivity; *Sp* specificity; ANC_0 absolute neutrophil count at day 0 (baseline) i.e. on the day of carboplatin administration; ANC_4 absolute neutrophil count at day 4; ANC_5 absolute neutrophil count at day 5. Prolonged neutropenia means a neutropenia lasting 3 days or more

negatives (specificity). Globally, ANC_0, ANC_4 and ANC_5 integrate the information about the shape and starting point of ANC-time profile following initiation of the chemotherapy. The reasons why the decision rules were not built in a sequential way were 1) to avoid the accumulation of decision error, and 2) to allow them to be used independently of each other. As with all model-based approaches, our decision rules are highly dependent on a set of assumptions which are largely discussed in a previous article (25).

Usual dosing times of G-CSF are 24 h or 24 to 72 h after the last day of chemotherapy for pegylated and daily formulations, respectively (30,31). Other schedules have been studied in humans and laboratory animals, and a delayed administration is suggested in some studies (32–35). However, the proof of the efficacy of a delayed G-CSF treatment is not well established. Here, the Monte Carlo simulations suggest that an administration of pegfilgrastim on D5 is as efficient as the conventional administration of pegfilgrastim D1. Pegfilgrastim was chosen over filgrastim for the Monte Carlo simulation studies because previous clinical studies have reported equivalent or better efficacy for the pegylated formulation (36–38). The choice of D5 was made as follows. 1) We had to choose one time, late enough after baseline, to correctly allow the identification of at risk patients: when the chosen time get closer to the nadir, the estimate of the decrease rate of ANC becomes better. 2) The time of administration of G-CSF (which is necessarily posterior to the last sampling time) must not be too close to the nadir, if not the G-CSF administration would be without effect (too late). The time of nadir for neutropenia after an administration of carboplatin is frequently later than with other cytotoxic drugs (14–28 days *vs.* 7–10 days). Because carboplatin was associated with other drugs for most of the patients in our study, the nadir could be expected earlier. Several days of administration have been tried and D5 appeared to be the day with the best result between these 2 constraints.

Clearly, the systematic use of prophylactic G-CSF therapy is controversial given its cost and potential side effects (9). In our simulation studies, we found that pegfilgrastim did not prevent prolonged high grade/severe neutropenia in all the patients. More precisely, about half of the patients experiencing high grade neutropenia without G-CSF did not benefit from G-CSF administration on D5. This finding is consistent with literature data: indeed, several studies (8–10,30) reported

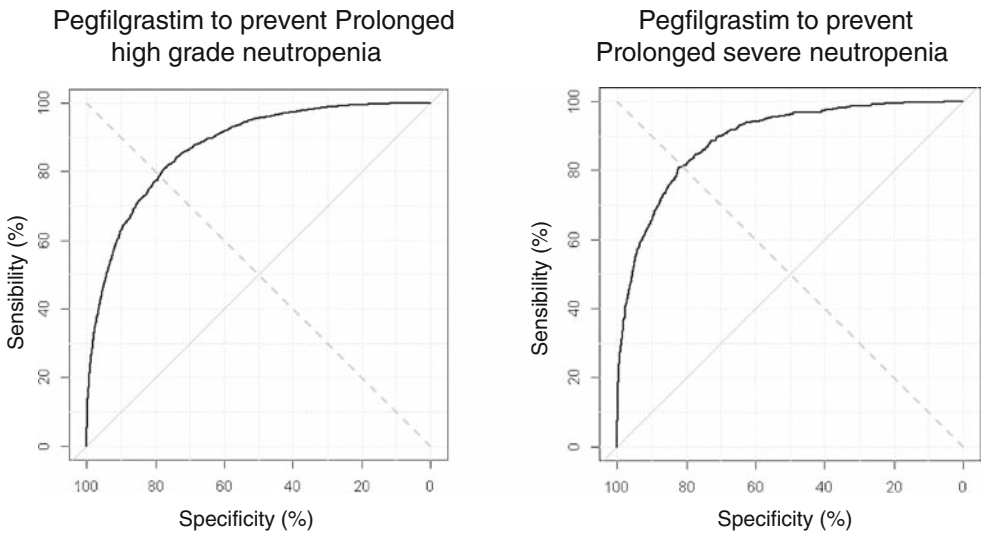

Fig. 4 Receiver-operating characteristic curves for the decision rules to identify for whom G-CSF administration at day 5 would prevent prolonged (at least 3 days) neutropenia at cycle 1. *Left* ROC curve for the prediction of the prevention of high grade neutropenia, i.e., grade 3 and 4; *right* ROC curve for the prediction of the prevention of severe neutropenia, i.e., grade 4. In all cases, the predictors were ANC on day 0 (ANC_0), day 4 (ANC_4) and day 5 (ANC_5).

Table III Decision Rules to Identify Patients for Whom G-CSF Administration at Day 5 Would Prevent Prolonged High Grade Neutropenia. Prolonged Neutropenia Means a Neutropenia Lasting for 3 Days or More. G-CSF is Given as Pegfilgrastim (Single 6-mg Dose by Subcutaneous Route). The Patient Would Benefit from G-CSF Administration When the Decision Rule Equation Gives a Positive Value

Prediction of beneficial effect of pegfilgrastim regarding	Decision rule equations with 2 or 3 early ANCs	Se/Sp
Prolonged grade 3–4 neutropenia	$-0.758-0.092\times\log(ANC_0)-1.243\times\log(ANC_5)>0$	0.69/0.70
	$2.727-0.009\times\log(ANC_0)-0.789\times\log(ANC_4)$ $-0.877\times\log(ANC_5)>0$	0.73/0.73
Prolonged grade 4 neutropenia	$-1.429-0.061\times\log(ANC_0)-1.759\times\log(ANC_5)>0$	0.76/0.76
	$3.171+0.128\times\log(ANC_0)-0.930\times\log(ANC_4)$ $-1.416\times\log(ANC_5)>0$	0.79/0.79

Se sensitivity; *Sp* specificity; *ANC*0 absolute neutrophil count at day 0 (baseline) i.e. on the day of carboplatin administration; *ANC*4 absolute neutrophil count at day 4; *ANC*5 absolute neutrophil count at day 5

that G-CSF only reduced the occurrence of chemotherapy-associated febrile neutropenia but did not prevent febrile neutropenia or infections in all the patients. This is the reason why we propose another set of decision rules to guide G-CSF prophylactic use for the first cycle.

Arbitrarily, we have chosen to establish decision rules that achieve similar sensitivity and specificity, but from a clinical point of view, predictive positive/negative values are the sole criteria of interest. Recall that the predictive positive value is the probability to experience the event that the decision rule aims to predict when the decision rule gives a positive result. Inversely, the predictive negative value is the probability to not experience this event when the decision rule gives a negative result. The higher the sensitivity and specificity, the higher the predictive values. For all the decision rules proposed in the article, both sensitivity and specificity were above 70% (and close to 80% in most cases). Predictive values also depend on the pre-test probability which is the probability for a given patient to experience the targeted event. This pre-test probability is driven by the clinician's evaluation of the patient taking into account the available guidelines. From a medical point of view, the negative predictive value is of major interest in our case. Indeed, we do not want the decision rules to miss patients that would need G-CSF. If we consider as an example a pre-test probability of 20% (i.e. the threshold in EORTC guidelines) and a sensitivity/specificity of 80%/80%, we obtain a negative predictive value of 94%. From an economical point of view, it would be more interesting to increase the predictive positive value. It is possible to optimize one of these two aspects (clinical or economical) using other decision rules leading to different sensitivity and specificity.

The proposed decision rules should be used in complement of the EORTC guidelines, which allow the identification of patients with high risk of febrile neutropenia, but not of prolonged high grade neutropenia. The prediction of prolonged high grade neutropenia relies essentially on the rate at which ANC decrease. In this respect, the knowledge of ANC only at baseline does not give any information about this rate and consequently does not improve the identification of patients experiencing prolonged high grade neutropenia. Blood sampling at D4 and D5 could be performed only in patients identified at risk of febrile neutropenia regarding EORTC guidelines. We are aware that obtaining 3 blood samples in the same week for a patient could be difficult. However, this could be valuable for patients at risk and sampling at D4 and D5 could be performed in a local medical laboratory. The decision rules could also be derived from 2 ANCs (D0 and D5), which would be more convenient for patients and clinicians, but the performances are a less good.

Among the 10500 virtual patients used to derive the decision rules, 32% received multiple corticosteroid doses and the others not. The proposed decision rules are then practicable regardless of multiple corticosteroid administration. Nevertheless, those decision rules might be biased toward the group of patients with no multiple corticosteroid administration. The performances of the decision rules should be even better by deriving specific equations for each sub-group of patients. However, our primary objective was to propose this new approach and not to derive all possible decision rules, which would have been extremely tedious.

Note that ANC used in logistic regression and decision rules were simulated with residual error to carry out logistic regression analyses and establish decision rules. Residual error accounts both for measurement error and model misspecification. Since the measurement error depends only on (pre)analytical performance, we believe that the sensitivity and the specificity of the proposed decision rules could be increased with good clinical practice.

There are major assumptions made in this article. Firstly, the estimated drug effect for carboplatin is not a pure carboplatin drug effect as the majority of patients received various combination therapies. However, as it has been shown in the previous paper the effect of such associations on ANC profiles remains not significant (non significant covariate). Of course, the impact of other associations than those used in this study should be investigated. Secondly, an important limitation of our model is that G-CSF pharmacokinetic parameters were assumed to be identical in healthy volunteers and cancer

patients. It is likely that among cancer patients receiving carboplatin, some may suffer from renal insufficiency since carboplatin is administered in place of cisplatin which cannot be administered to renally impaired patients. Thus, a smaller k_{el} may be encountered in cancer patients treated with carboplatin, resulting in higher G-CSF circulating concentrations and possibly in different nadir values. Prospective studies are then needed to confirm this assumption. Finally, the nonlinear component of G-CSF clearance shall involve the whole pool of G-CSF receptors in the body, which is not the case in our model. In the model of Krzyzanski *et al.* (29). the amount of receptors per cell ξ was assumed to be approximately identical for each compartment. However, the model of Krzyzanski *et al.* (29) did not provide a very good description of our data and a much better fitting was obtained when considering R_{tot} proportional to the amount circulating neutrophils. We attempted to re-estimate the ξ value in addition to other parameters ($E_{max}1$, $k_{el}1$) but whatever the model tested, we always faced irrelevant predictions. All these issues have already been discussed in details in the previous paper as potential limitations of our model.

The prevention of febrile neutropenia is a critical point for the oncologists. This could be reached by early predicting and avoiding prolonged high grade neutropenia. As stated in the introduction, several guidelines have been proposed to compute the individual risk of experiencing febrile neutropenia (3,14,15). This risk is calculated from covariates such as tumor type, chemotherapy regimen and patient-related risk factors (age, gender, stage, previous febrile neutropenia, comorbidities, performance/nutritional status). In population PK/PD modeling, it has been shown that covariate-based individual predictions can be refined substantially by taking into account the first observations in the patient (21,22). This strategy relies on individual model predictions and has been widely applied to adjust chemotherapy dosing regimen (39–43). Briefly, the dose of cytotoxic drug at cycle 1 is adjusted on patient's characteristics (body surface area, or renal covariates for carboplatin) and is further refined at cycle 2 using blood cell counts at cycle 1. Here, we globally use the same approach but apply it to G-CSF in order to prevent prolonged high grade neutropenia at cycle 1, i.e., the most critical period with respect to febrile neutropenia events (20,23,24). We acknowledge that patients experiencing prolonged high grade neutropenia do not systematically present febrile neutropenia. However, prevention of prolonged high grade neutropenia avoids a significant number of febrile neutropenia events.

There were mainly two kinds of decision rules: 1) decision rules requiring a modeling approach to predict the whole time course of ANC for each patient from its available ANCs; 2) decision rules that does not require modeling approach. These decision rules try to identify the times of blood sampling that best predict neutropenia. We have chosen the second approach because a) it gives better results than the first one b) it is easier to use for clinicians c) the first one undoubtedly relies on predicted individual parameters with shrinkage. Obviously, the proposed decision rules where derived based on simulated ANC. But they should be used with the observed ANCs of the patient, whereas in model-based approach, individual PK/PD parameters are necessarily predicted and thus potentially imprecise and biased.

CONCLUSION

While our approach is innovative, our findings need to be confirmed by prospective studies for carboplatin and other cytotoxic drugs and other aspects of toxicity might be investigated. It is clear that our model relies on previous knowledge and assumptions that need to be further documented. Once validated, the proposed decision rules are easy to use by oncologists in their clinical practice. They aim to identify patients at risk for experiencing high grade neutropenia and guide the prophylactic use of G-CSF administration during the first cycle. They are therefore complementary to the existing general guidelines around the prediction of febrile neutropenia risk and the prophylactic use of G-CSF.

NOTATION SECTION

Abs_1	Absorption compartment for filgrastim/lenograstim
Abs_2	Absorption compartment for pegfilgrastim
ANC	Absolute neutrophil count (ANC_i: ANC at day i)
Base	Baseline level of absolute neutrophil count
C_{carbo}	Ultrafiltrable circulating concentration of carboplatin (plasma)
C_u	Free circulating concentration controlling G-CSF effects on bone marrow, calculated as the sum of non-pegylated and pegylated G-CSF free circulating (serum) concentrations
C_{tot}	Total circulating G-CSF concentration
Circ	Circulating mature neutrophil count (=*ANC*)
$E_{max}1$	Maximal effect of non-pegylated or pegylated G-CSF on proliferation
$E_{max}2$	Maximal effect of non-pegylated or pegylated G-CSF on maturation
$EC_{50}1$	Value of C_u eliciting 50% of the maximal effect on proliferation
$EC_{50}2$	Value of C_u eliciting 50% of the maximal effect on maturation
$F1(F2)$	Absolute bioavailability of filgrastim/lenograstim(pegfilgrastim) after subcutaneous administration (which, in the model, is taking into account via the apparent volume of distribution)

k	Transit rate constant between compartments of granulopoiesis (function of Cu) ($k = k_{tr} \times \left(1 + \frac{E_{max}2 \times C_u}{EC_{50}2 + C_u}\right)$)
$k_a1\,(2)$	Absorption rate constant for filgrastim/lenograstim(pegfilgrastim)
k_{circ}	Rate constant of elimination of neutrophils from the systemic blood circulation
K_D	Dissociation constant of RC complex ($= k_{off}/k_{on}$)
$k_{el}1$	Rate constant for the linear, non-specific elimination of endogenous G-CSF and filgrastim/lenograstim
$k_{el}2$	Rate constant for the linear, non-specific elimination of pegfilgrastim
k_{GCSF}	Rate constant of endogenous G-CSF production
k_{int}	Rate constant for non-pegylated or pegylated G-CSF elimination after binding to receptors and internalization
k_{prol}	Proliferation rate constant
k_{tr}	"Virtual" transit rate constant when $C_u = 0$ (cf. k)
MTT	Mean transit time for maturing precursors in bone marrow ($MTT = 4/k_{tr} \times \left(1 + \frac{E_{max}2 \times C_u}{EC_{50}2 + C_u}\right)$)
$Prol$	Stem cell and progenitor cell count (i.e., proliferative cells) in bone marrow
R	Concentration in G-CSF receptors present on circulating neutrophils
RC	Concentration in bound G-CSF complex (pegylated and non-pegylated G-CSF)
R_{max}	Maximal amount of receptors involved in nonlinear, specific clearance of pegylated and on-pegylated G-CSF ($=R+RC$)
ROC	Receiver-operating characteristic
$Slope$	Sensitivity to carboplatin myelotoxicity
$Transit_{1,2,3}$	Maturating granulocyte precursor count in transit compartments 1, 2 and 3 respectively
$VD_a1\,(2)$	Apparent volume of distribution of G-CSF (pegylated G-CSF) after subcutaneous administration of filgrastim/lenograstim (pegfilgrastim) ($VD_{1(2)}/F_{1(2)}$)
ξ	Proportionality constant for the amount of G-CSF receptors per cell

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We have no competing interest to declare.

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