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Early Identification of Patients at Risk of Cabazitaxel-induced Severe Neutropenia

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Abstract

Background: Cabazitaxel frequently causes severe neutropenia. A higher cabazitaxel systemic exposure is related to a lower nadir absolute neutrophil count (ANC).
Objective: To describe the effect of cabazitaxel systemic exposure on ANC by a population pharmacokinetic/pharmacodynamic (POP-PK/PD) model, and to identify patients at risk of severe neutropenia early in their treatment course using a PK threshold.
Design, setting, and participants: Data from five clinical studies were pooled to develop a POP-PK/PD model using NONMEM, linking both patient characteristics and cabazitaxel systemic exposure directly to ANC.
Outcome measurements and statistical analysis: A PK threshold, predictive of severe neutropenia (grade $\geq$3), was determined using a receiver operating characteristic curve.
Results and limitations: Ninety-six patients were included with a total of 1726 PK samples and 1081 ANCs. The POP-PK/PD model described both cabazitaxel PK and ANC accurately. A cabazitaxel plasma concentration of >4.96 ng/ml at 6 h after the start of infusion was found to be predictive of severe neutropenia, with a sensitivity of 76% and a specificity of 65%.
Conclusions: Early cabazitaxel plasma levels are predictive of severe neutropenia. Implementation of the proposed PK threshold results in early identification of almost 76% of all severe neutropenias. If prospectively validated, patients at risk could benefit from prophylactic administration of granulocyte colony stimulating factors, preventing severe neutropenia in an early phase of treatment. Implementation of this threshold permits a less restricted use of the 25 mg/m^2 dose, potentially increasing the therapeutic benefit.
Patient summary: Treatment with cabazitaxel chemotherapy often causes neutropenia, leading to susceptibility to infections, which might be life threatening. We found that a systemic cabazitaxel concentration above 4.96 ng/ml 6 h after the start of infusion is predictive of the occurrence of severe neutropenia. Measurement of systemic cabazitaxel levels provides clinicians with the opportunity to prophylactically stimulate neutrophil growth.

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1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is the most advanced form of prostate cancer. Patients with mCRPC have a median overall survival (OS) of <20 mo after the first line of therapy that generally consists of docetaxel or an androgen receptor signaling inhibitor (ARSi) [1,2]. Upon progression of disease, the standard second-line chemotherapy is cabazitaxel. In the TROPIC phase 3 trial, cabazitaxel frequently caused grade ≥3 neutropenia (occurred in 82% of patients) and febrile neutropenia (8%). Seven out of 18 cabazitaxel-related deaths were caused by neutropenia or its consequences [3]. In an effort to reduce cabazitaxel toxicity, while maintaining treatment efficacy, a lower dose (20 vs 25 mg/m^2) was investigated in the PROSELICA and FIRSTANA phase 3 trials. The lower dose effectively decreased the occurrence of grade ≥3 neutropenia (42% vs 73% and 38% vs 71%) and febrile neutropenia (2% vs 9% and 2% vs 12%) [4,5].

These observations suggest a pharmacokinetic (PK)-pharmacodynamic (PD) relationship, which has been described earlier for systemic cabazitaxel exposure and a decrease in neutrophils in a small group of patients [6]. This supports the rationale for an individualized approach by therapeutic drug monitoring of cabazitaxel to improve its tolerability, while preserving efficacy. A population PK/PD model could serve to identify patients at risk of severe neutropenia at an early stage, who can consequently be treated prophylactically with granulocyte colony stimulating factors (G-CSFs). Here, we aim to develop a population PK/PD model to describe the effect of cabazitaxel exposure on absolute neutrophil count (ANC) and to apply this model to identify patients at risk of severe neutropenia.

2. Patients and methods

2.1. Patients

Data were pooled from five clinical studies in patients treated with cabazitaxel conducted and/or analyzed at the Erasmus Medical Center Cancer Institute (Rotterdam, The Netherlands). Two of these studies investigated whether the ARSi enzalutamide (CABENZA) [7] and darolutamide (CABADARO) [8] influenced cabazitaxel PK. A third study (CABARESC) addressed whether budesonide could reduce cabazitaxel-induced diarrhea [9]. A fourth study (CABA-V7) investigated the efficacy of cabazitaxel in patients positive for androgen receptor splice variant 7 (AR-V7) [10]. Furthermore, patients from a randomized phase 2 trial (CAINTA), designed to improve the clinical feasibility rate of cabazitaxel by PK-based dose adjustments during treatment, were included [11]. Collected data included cabazitaxel dosing schedule and dose, age, body weight, body surface area (BSA), World Health Organization performance status (WHO PS), laboratory values (ANC, albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase [ALT], lactate dehydrogenase, bilirubin, creatinine, leukocytes, thrombocytes, and hemoglobin), and cabazitaxel concentrations in plasma. All PK samples were analyzed at the translational pharmacology laboratory at the Erasmus Medical Center Cancer Institute using a validated liquid chromatography tandem mass spectrometry method, as described previously [12]. ANC values, obtained from 50 d prior to the first infusion until 50 d after the last infusion, were included. ANC values measured in the treatment cycle after administration of G-CSFs were excluded from the model-development dataset.

2.2. Population PK model development

The population PK analysis was performed using a nonlinear mixed-effect model approach with NONMEM version 7.5 (ICON; Development Solutions, Ellicott City, MD, USA) and Pirana software version 3.0.0 (Certara, Princeton, NJ, USA). Initially, the three-compartmental model structure of Ferron *et al.* [13] was used to describe the data. Thereafter, different structural model components were evaluated. These included four- and two-compartment models, different interindividual variation (IIV) models on various parameters, different interoccasional variation (IOV) models, and diverse error models, stratified per study. If the model estimates were unstable, the data were transformed using the natural logarithm. All models were evaluated numerically using the difference in objective function value (ΔOFV; $p < 0.05$, chi-square test), relative standard error (<50%), shrinkage (<35%), and the condition number (<1000). Visual evaluation was performed using goodness-of-fit (GOF) plots and visual predictive checks (VPCs).

After obtaining a stable model that best described cabazitaxel PK, covariates were added to further explain differences in IIV and IOV, in which a PK cycle was defined as an occasion. Continuous covariates (age, BSA, weight, and collected laboratory values) were centered around the median and added as power models. Categorical covariates (WHO PS and use of a concomitant CYP3A4 inducing agent) were tested as proportional models. The analysis was executed using forward inclusion ($p < 0.05$, chi-square test) and backward elimination ($p < 0.01$, chi-square test) [14]. The final structural model with additional covariates was evaluated using the automated sampling importance resampling (SIR) procedure [15].

2.3. PK/PD cabazitaxel-neutrophil model

The validated PK model parameters were fixed on an individual basis during PD model development. In case of model instability, the PD data were transformed logarithmically. First, the structural model as developed by Friberg *et al.* [16] was fitted to the dataset. Thereafter, the number of transit compartments was evaluated. Both a linear and an E_{max} model were evaluated to test which best described the relationship between cabazitaxel exposure and ANC. After obtaining a structural model that adequately described the data—evaluated according to the same criteria as the PK model—covariates were tested to explain IIV. The covariates tested to explain IIV were WHO PS, age, BSA, and albumin serum concentrations, as these were incorporated in earlier models [17]. The model was validated using an automated SIR procedure.

Next, a PK threshold was determined that could predict the occurrence of severe neutropenia, that is, grade ≥3

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(ANC <1.0 × 10^9/l), according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [18]. A cohort of 1000 patients was simulated, of whom 50% received 25 mg/m^2, whereas the other half received 20 mg/m^2. Covariates were imputed using the distribution in the model-development cohort. Predicted ANCs at nadir were used to determine the occurrence of severe neutropenia. The predicted cabazitaxel plasma concentrations at various time points (5, 6, 7, 8, 12, 24, 48, and 72 h after the start of infusion) were used to determine which time point was most predictive. This was quantified using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. As earlier samples are more convenient for both the patient and the laboratory, the AUC had to be improve by ≥1% per subsequent time point. Thereafter, the best threshold at the most predictive time point was determined using Youden's J statistics [19].

3. Results

3.1. Patient characteristics

After data pooling, a total of 1776 PK samples from 96 patients were available for an analysis. Of these, 50 samples from 19 patients were excluded for suspected erroneous sampling registration, quantification, or plasma withdrawal. After exclusion of 39 ANCs, which were measured after G-CSF administration, 1081 ANCs were available for the PK/PD model-development dataset. Patient characteristics are shown in Table 1. Patient characteristics stratified per study are shown in Supplementary Table 1.

Table 1 – Patient, treatment, and sampling characteristics prior to the first cabazitaxel infusion

	Variable (n = 96)	Median/ n	Range/ %
Population	Age (yr)	69	46–78
	Weight (kg)	86	60–129
	BSA (m^2)	2.04	1.69–2.54
	WHO PS		
	0	30	31%
	1	63	66%
	2	1	1%
	Unknown	2	2%
First cycle			
	20 mg/m^2	18	19%
	AUC (mg × h/ml)	1.11	0.66–2.08
	25 mg/m^2	78	81%
	AUC (mg × h/ml)	1.33	0.61–2.57
Laboratory values	Albumin (g/l)	40	31–49
	ALK-P (U/l)	126	28–1502
	ALT (U/l)	16	5 – 97
	AST (U/l)	26	10–166
	Bilirubin (μmol/l)	6	2–15
	Creatinine (μmol/l)	75	45–147
	eGFR (ml/min)	89	41–>90
Hematology values	ANC (×10^9/l)	5.1	2.0–10.6
	Leukocytes (×10^9/l)	7.3	2.8–15.7
	Hemoglobin (mmol/L)	7.6	5.2–9.0
Samples	PK observations	1726	
	Treatment cycles with PK/patient	2	1–7
	Samples/cycle	11	3–12

ALK-P = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; AUC = area under the curve for the first cycle; BSA = body surface area; eGFR = estimated glomerular filtration rate (obtained using the Chronic Kidney Disease Epidemiology Collaboration equation); PK = pharmacokinetics; WHO PS = World Health Organization performance status.

3.2. Population PK analysis

A three-compartment population PK model best described cabazitaxel PK (Fig. 1). Data were transformed using a natural logarithm. IIV was included for clearance, the intercompartmental clearance between the central compartment toward the first peripheral compartment, and the distribution volume of the central compartment.

A separate error for data originating from the CAINTA study lowered the conditional number to <1000. The IOV was not included in the final model due to a high residual error and high shrinkage on the IOV parameter.

Four covariates were included in the final model. A higher BSA (p < 0.001), WHO PS ≥1 (p = 0.003), and concomitant therapy with enzalutamide (p < 0.001), a strong CYP3A4-inducer, was correlated with increased cabazitaxel clearance, whereas an increase in ALT decreased cabazitaxel clearance (p < 0.001). The other covariates did not significantly affect cabazitaxel PK. Parameter estimates and visual evaluations of the PK model are depicted in Supplementary Table 2 and Supplementary Figures 1–3.

3.3. PK/PD cabazitaxel-neutrophil model

The structural model adequately described the ANC over time and resulted in a stable model. The linear concentration-effect model was implemented, as this model was more stable than an E_{max} model and performance was similar. Parameter estimates for the PK/PD model are depicted in Supplementary Table 2. See Figure 1 for the schematic representation of the structural PK/PD model. Varying the number of transit compartments did not improve the model significantly.

After obtaining a valid structural model, covariates were included in the model. Older patients were found to have a higher slope (p < 0.001), meaning that the drop in ANC is more profound than in a younger patient with a similar exposure. A high serum albumin level was also associated with a lower slope (p < 0.001). However, this was excluded as two patients caused this significant effect (p = 0.034 without these two patients). In addition, inclusion of the effect of serum albumin levels on slope deteriorated model performance in more than half of patients. BSA explained variability in baseline ANC, with a higher BSA being associated with a lower baseline ANC level (p = 0.003). Nonetheless, cabazitaxel systemic exposure remained the most important factor in determining ANC. VPCs, GOF plots, and numerical evaluations confirmed model performance (Supplementary Figs. 2, 4, and 5). Applying the PK/PD model to a patient, illustrated model performance and indeed revealed both a lower predicted and observed nadir ANC in case of a higher cabazitaxel dose, and thus higher exposure (Fig. 2). In Figure 3, the effect of a higher dose and the effect of

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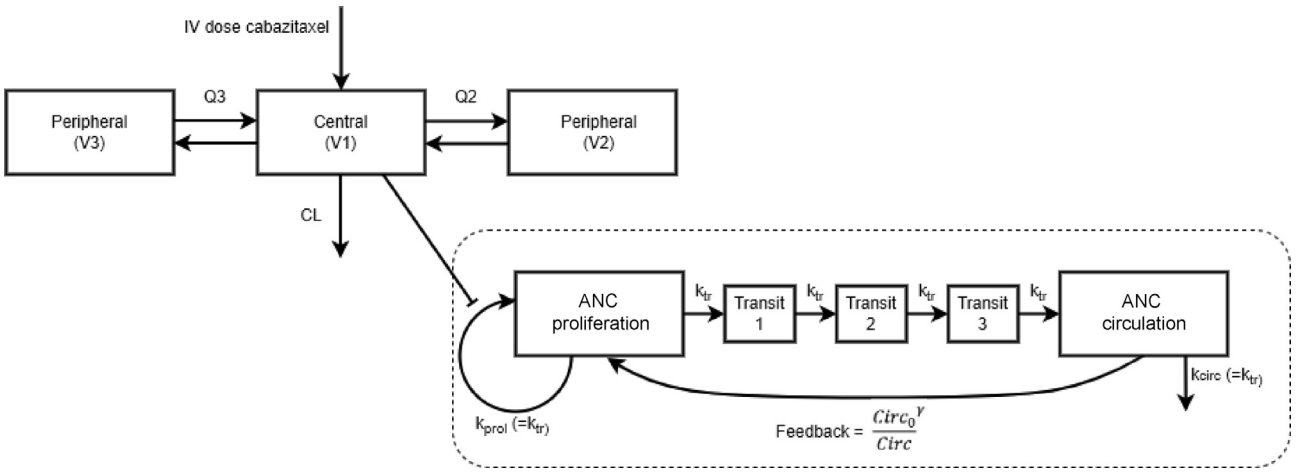

Fig. 1 – Schematic representation of the PK/PD model of cabazitaxel and ANC. The model structure at the top left depicts the population PK model. The model structure inside the dashed line represents the PD model. The inhibitory effect of cabazitaxel exposure is depicted as a line with a flat end and impacts the proliferation rate k_{prol}. ANC = absolute neutrophil count; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic.

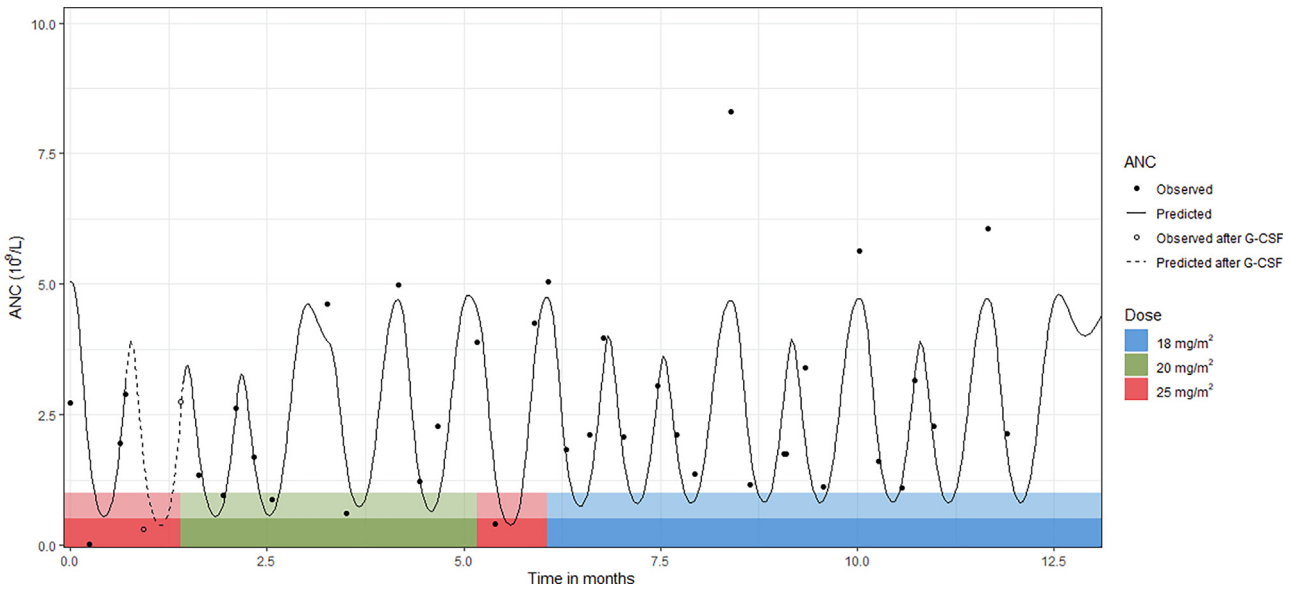

Fig. 2 – Observed and predicted ANCs over the course of cabazitaxel treatment in a patient. The colored line expresses both the relative dose and the severity of neutropenia, with the upper band set to grade 3 (ANC <1.0 × 10^9) and the lower band set to grade 4 neutropenia (ANC <0.5 × 10^9). The dashed line depicts the model prediction after G-CSF administration. ANC = absolute neutrophil count; G-CSF = granulocyte colony stimulating factor.

covariates are demonstrated in a simulated patient, also showing that the predicted nadir ANC occurs approximately 11 d after cabazitaxel administration.

The AUCs of the ROC curves for the plasma concentration of cabazitaxel at various time points were within a 2% range (74.6–76.6%). The best threshold was determined to be 4.96 ng/ml 6 h after the start of infusion. This resulted in an AUC of 75.9%, a sensitivity of 76%, and a specificity of 65% (Supplementary Fig. 6). Since drawing a blood sample at exactly the right moment is challenging in clinical practice, the possibility to extrapolate a plasma concentration at another timepoint may be useful. At 6 h after the start of administration, the cabazitaxel half-life is 6.4 h. Using equation 1, the cabazitaxel concentration can be extrapolated toward the correct time point [20]. As the decline in cabazitaxel concentrations is 5% after 28 min, we expect this extrapolation method to be feasible within a 30-min time window.

Equation 1: extrapolation of cabazitaxel concentrations:

$$C_e = C_t * \exp\left(\frac{-0.693 * \Delta t}{6.4}\right)$$

C_e: extrapolated concentration; C_t: measured concentration at time point t; Δt: difference in time between C_e and C_t in hours; 6.4: half-life of cabazitaxel in hours at approximately 6 hours after the start of infusion.

When applying the threshold to a simulation cohort, 48.5% of patients were identified to be at risk of severe neutropenia. Of these, 53.0% were predicted to experience severe neutropenia, while 16.1% of patients below the proposed threshold were predicted to encounter severe neutropenia. In addition, 81.3% of all predicted grade 4 neu-

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tropenia cases were found to be above the threshold (Fig. 4A). When applying this threshold to the model-development cohort, similar performance was obtained (Fig. 4B).

4. Discussion

In this study, a PK/PD model to describe the effect of cabazitaxel systemic exposure on ANC was developed, and a PK threshold was determined to predict the occurrence of severe neutropenia. Based on the cabazitaxel concentration in a single blood sample, withdrawn 6 h after cabazitaxel administration, a rapid determination of a patient's risk for severe neutropenia can be realized.

To date, no consensus on an optimal starting dose for cabazitaxel has been achieved. Although subanalyses of PROSELICA did not identify patient subgroups in favor of the 25 mg/m^2 dose, post hoc analyses from FIRSTANA and PROSELICA suggested that patients with pain progression at baseline showed increased OS after treatment with 25 mg/m^2 compared with 20 mg/m^2 [21,22]. Yet, the 20 mg/m^2 dose is used most commonly out of concern of hematologic toxicity, possibly not fully exploiting the therapeutic potential of cabazitaxel. Contrarily, in the CARD trial, a 25 mg/m^2 dosing regimen with prophylactic G-CSFs following each administration was applied, assuring maximal treatment efficacy and safety [23]. To avoid the medical and economic burden of unconditional prophylaxis in every patient, yet facilitating the option of a higher dose, the tool presented here offers a solution. Immediate prediction of a patient's risk for severe neutropenia by a single sample enables targeted prophylactic stimulation of granulocyte colonies early in the treatment course, ultimately prevent-

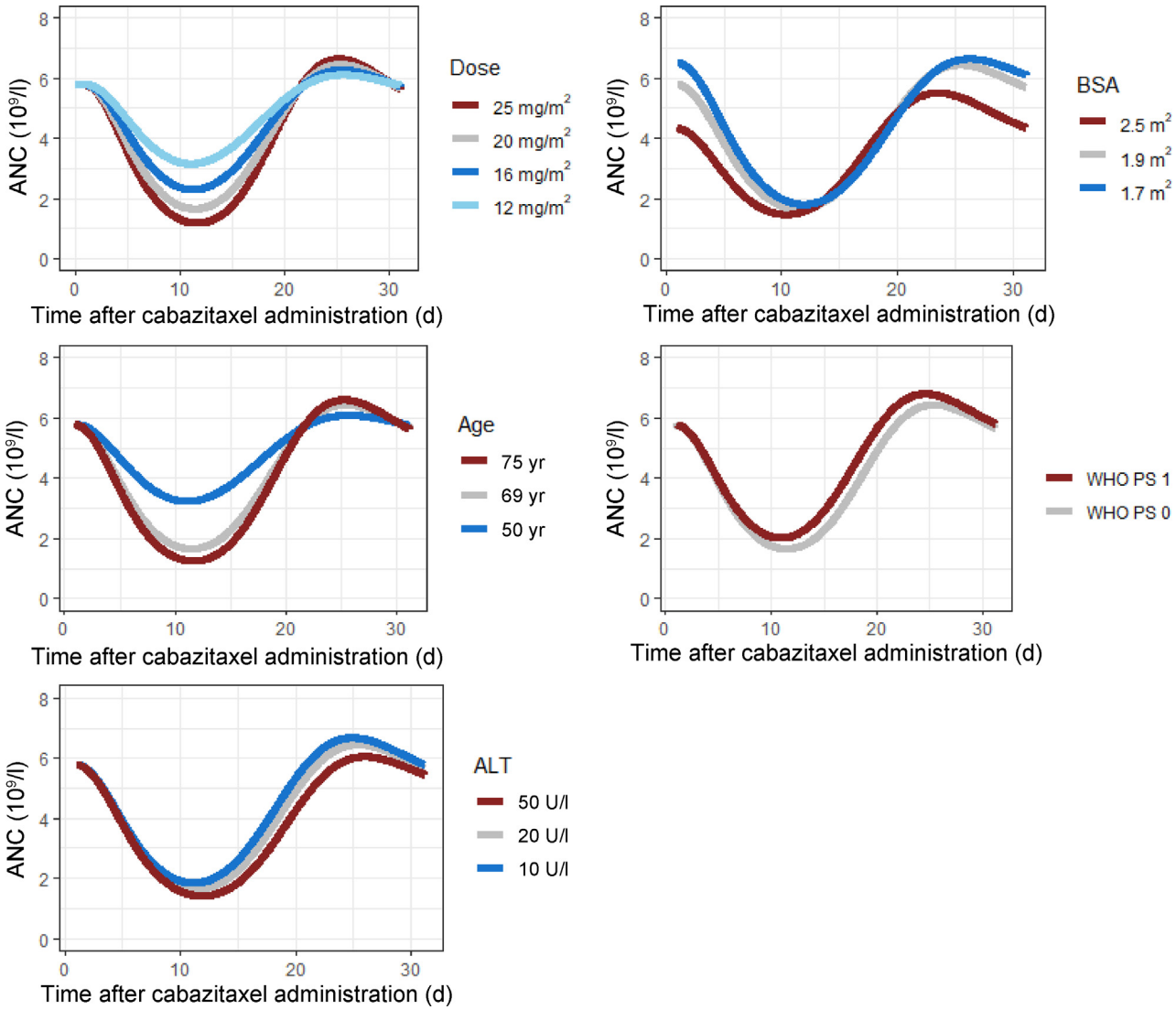

Fig. 3 – Simulation of ANC over the course of one cabazitaxel treatment cycle for typical patients with different characteristics. The reference patient (gray line) is 69 yr old, with a BSA of 1.9 m^2, a WHO performance score (PS) of 0, and a serum alanine transaminase level (ALT) of 20 U/l, and received a cabazitaxel dose of 20 mg/m^2, which is similar to the medians in the model-development population. ANC = absolute neutrophil count; BSA = body surface area; WHO PS = World Health Organization performance status.

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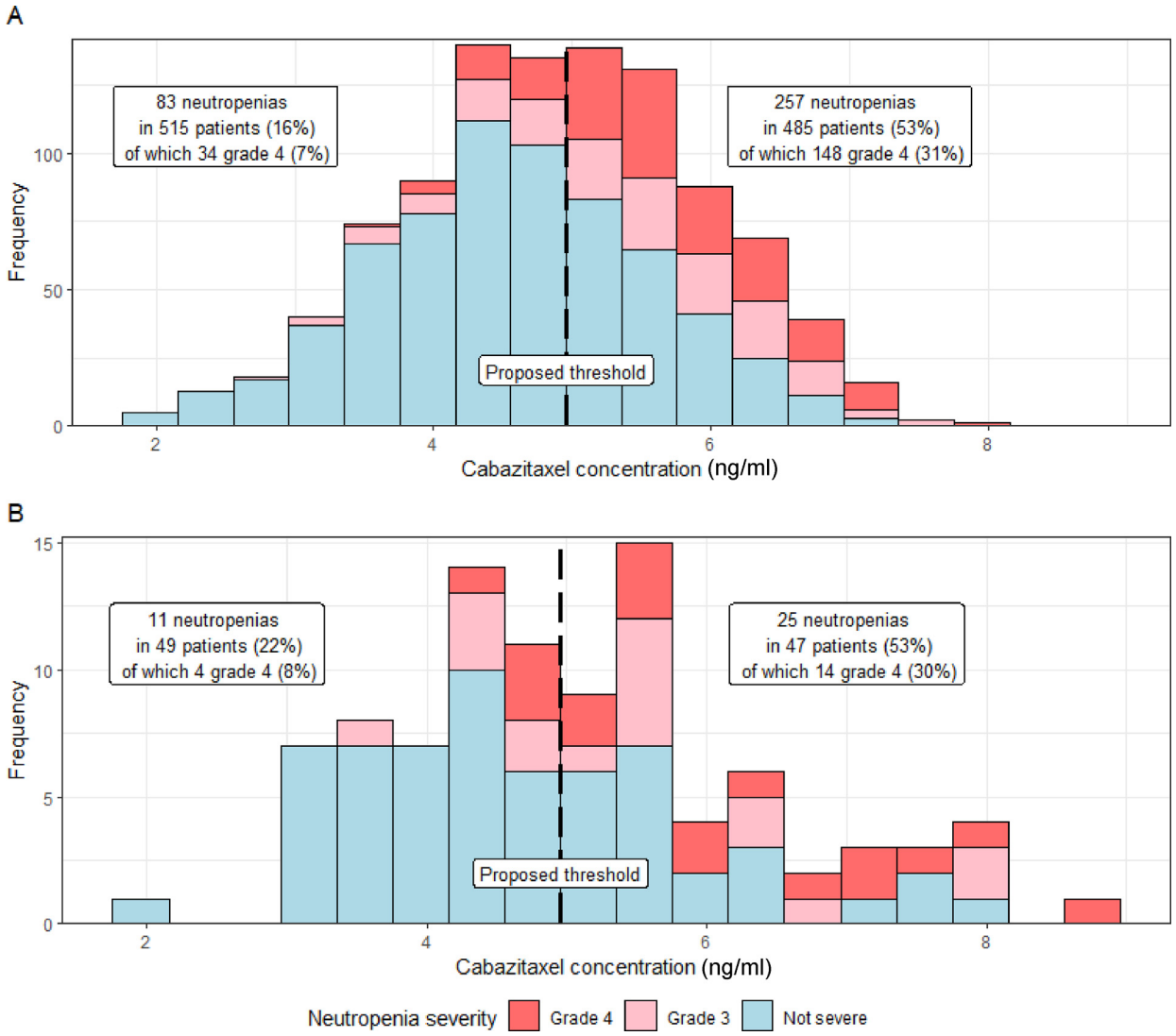

Fig. 4 – Exploration of the impact of implementing a pharmacokinetic threshold on identifying severe neutropenia (A) in a simulated cohort (*n* = 1000) and (B) in the real-world model-development cohort.

ing severe hematologic toxicity. Likewise, patients at a low risk for severe neutropenia can be identified, warranting safe administration of the 25 mg/m^2 dose.

Our PK approach for predicting severe neutropenia during cabazitaxel treatment has several advantages over conventional ANC determination. First of all, the early assessment of patients at risk of severe neutropenia—namely, the day after cabazitaxel administration—permits immediate decision-making to prevent severe neutropenia or to reduce its severity early in the treatment course. Quantification of cabazitaxel in a plasma sample can be accomplished in only a few hours, facilitating prophylactic G-CSF administration, which should be administered 1–3 d after cabazitaxel infusion [12,24]. Second, conventional sampling is easily prone to an information bias as a result of inaccurate sampling time relative to the nadir ANC. For example, in Figure 2 at the 5-mo time point, the ANC was unknowingly determined before and after the nadir, failing to detect the predicted grade 3 neutropenia. This was followed by the clinical decision of a dose increase, ultimately leading to a grade 4 neutropenia in the next treatment cycle. In contrast, our model-based method provides reliable predicted ANCs on a continuous timescale, including the clinically relevant nadir, and could support clinical decision-making. Finally, the need for repetitive sampling in order to obtain ANCs would become redundant after implementation of the PK/PD model and would be substituted by a single blood withdrawal for the PK analysis.

Next to G-CSF administration, reducing the cabazitaxel dose in the subsequent cycle is also an option to prevent neutropenia. However, severe neutropenia during the first cycle may still occur, requiring G-CSF administration. Importantly, the risk of febrile neutropenia is at its highest after a patient's first cabazitaxel administration, underscoring the high value of applying an intervention during the first treatment cycle [25]. Moreover, a dose reduction may also compromise treatment efficacy, especially since the occurrence of neutropenia grade ≥3 was found to be associated with improved OS in mCRPC patients receiving cabazitaxel [26].

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To date, two different population PK models have been developed to describe the PK of cabazitaxel [13,27]. The structural model presented in this paper was identical to the model by Ferron *et al.* [13]. Both published models, and our model included BSA as a covariate on cabazitaxel clearance. Moreover, patients with WHO PS $\geq$ 1 showed higher clearance than those with WHO PS 0. In our model, concomitant treatment with the CYP3A4 inducer enzalutamide increased clearance, whereas an increase in ALT decreased clearance, which is indicative of liver damage [28]. The other tested covariates did not impact cabazitaxel PK significantly. However, any influence of these covariates, such as estimated glomerular filtration rate (eGFR), could not be excluded by the model due to a lack of low eGFR values in the population.

In the PD model, a higher BSA was associated with a lower baseline ANC. This is in agreement with the finding that a BSA of $\geq$2 m^2 is a risk factor in men for developing myelosuppression after antineoplastic treatment [29,30]. Additionally, our model showed that older patients are more vulnerable to neutropenia due to a higher slope, which is a common feature described already in guidelines [24]. When comparing the PK/PD model with the model for docetaxel developed previously by Friberg *et al.* [16], the baseline ANC is similar (5.1×10^9/l vs 5.5×10^9/l), whereas the drop in ANC is delayed in patients treated with cabazitaxel (mean transit time = 89 vs 110 h). In addition, the additional error (1.15×10^9/l vs 0.70×10^9/l) and the proportional error (27.3% vs 16.4%) are lower for the cabazitaxel model, indicating a stable PK/PD model that describes the ANC over the course of treatment well [16].

Strengths of the study are the population PK approach, which allows a direct association between cabazitaxel plasma concentrations and ANC values during the course of therapy. In addition, we obtained a large and dense dataset containing relevant covariates and ANCs throughout the treatment. This resulted in a stable model with a low residual standard error on the parameter estimates. Furthermore, all tested covariates are easy to obtain, facilitating implementation of the model by others for quantification of exposure or prediction of cabazitaxel plasma concentrations. The current study also poses some limitations. As data originated from the standard-of-care treatment, ANCs were mostly collected just prior to the next infusion or when a patient encountered adverse effects. This could lead to an information bias. However, the structural, weekly determination of ANCs of patients in the CAINTA trial counteracted this. Moreover, PK data for a number of patients were obtained only for a single treatment cycle. This could affect the PD model that was fitted over data of the whole treatment period, by ignoring changes in PK not accounted for by covariates. Yet, when inspecting data from patients with many PK cycles, no gradual decline or increase in cabazitaxel exposure was observed.

5. Conclusions

In conclusion, a population PK/PD model describing the relationship between cabazitaxel exposure and ANC was developed. This model was subsequently used to identify a PK threshold to identify patients at risk of severe neutropenia. This threshold facilitates rapid initiation of prophylactic G-CSFs to reduce the occurrence of severe neutropenia.

Author contributions: Bram C. Agema had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Agema, Buck, Sassen, de Wit, Koolen, Mathijssen.
Acquisition of data: Agema, Buck, Viskil, Isebia, de Neijs, Joerger, Koolen, Mathijssen.
Analysis and interpretation of data: Agema, Buck, de Wit, Koolen, Mathijssen.
Drafting of the manuscript: Agema, Buck, de Wit, Koolen, Mathijssen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Agema, Viskil, Sassen.
Obtaining funding: Mathijssen.
Administrative, technical, or material support: Agema, Buck, Viskil, Isebia, de Neijs.
Supervision: Koch, de Wit, Koolen, Mathijssen.
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Appendix A. Supplementary data

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