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RESEARCH PAPER

Exposure to Docetaxel in the Elderly Patient Population: a Population Pharmacokinetic Study

Marie-Rose B. S. Crombag[1,2] • Thomas P. C. Dorlo[1,2] • Ellen van der Pan[2] • Anoek van Straten[2] • Andries M. Bergman[3] • Nielka P. van Erp[4] • Jos H. Beijnen[1,2,5] • Alwin D. R. Huitema[1,2,6]

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ABSTRACT

Background Docetaxel is commonly used in elderly patients, who are frequently diagnosed with prostate cancer. Although previous studies revealed no clinically relevant impact of older age on docetaxel pharmacokinetics (PK), this may be masked by indication. Metastatic castration-resistant prostate cancer (mCRPC) patients were reported to have approximately two-times lower systemic exposure compared to patients with other solid tumors. This study assessed the impact of older age on docetaxel PK, also considering the effect of indication on docetaxel PK.

Methods Prospectively collected docetaxel PK data from patients aged ≥70 was pooled with PK data from an earlier published multicenter study. A 3-compartment population PK model, including multiple covariates, was used to describe docetaxel plasma concentration-time data. We added the effect of prostate cancer (mCRPC and metastatic hormone-sensitive prostate cancer (mHSPC)) on clearance to this model. Hereafter, we evaluated the additional impact of older age on docetaxel clearance, using a significance threshold of $p < 0.005$.

Results Docetaxel plasma concentration-time data from 157 patients were analyzed. Median age in the total cohort was 67 years (range 31-87), with 49% of the total cohort aged ≥70. The impact of age on docetaxel clearance was statistically significant ($p < 0.005$). For a typical patient, a 10-year and 20-year increase of age led to a reduction in clearance of 17% and 34%, respectively.

Conclusion In this cohort study, age significantly and independently affected docetaxel clearance, showing lower docetaxel clearance in elderly patients. In our cohort, mCRPC and mHSPC patients both had higher clearance than patients with other solid tumors.

Key Points
- Older age significantly influenced docetaxel clearance
- mCRPC and mHSPC patients both had higher clearance than patients with other solid tumors
- Regardless of the impact of prostate cancer, older age was a significant determinant for docetaxel clearance

✉ Marie-Rose B. S. Crombag
m.crombag@nki.nl

1 Department of Pharmacy & Pharmacology
Antoni van Leeuwenhoek – Netherlands Cancer Institute
Plesmanlaan 121, 1066, CX Amsterdam, the Netherlands

2 Division of Pharmacology
Netherlands Cancer Institute
Amsterdam, the Netherlands

3 Division of Medical Oncology, The Netherlands Cancer Institute
Amsterdam, The Netherlands

4 Department of Pharmacy and Radboud Institute of Health Sciences
Radboud University Medical Center
Nijmegen, the Netherlands

5 Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University
Utrecht, the Netherlands

6 Department of Clinical Pharmacy, University Medical Center Utrecht
Utrecht University
Utrecht, the Netherlands

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INTRODUCTION

Docetaxel is a frequently used chemotherapeutic agent to treat a variety of solid tumors. It is a lipophilic drug that is highly protein bound to *e.g.* alpha-1-acid glycoprotein (AAG) and albumin (1,2). Multiple factors appeared to influence docetaxel clearance including body surface area (BSA), hepatic impairment, plasma proteins, drug transporters, metabolizing enzymes, smoking, and hormonal status (3,4). Docetaxel exposure shows large interpatient variability, hence several

studies evaluated multivariate models to establish predictors of clearance to ultimately improve treatment outcome (4,5). With increasing age, altered exposure may be expected due to differences in *e.g.* body composition, levels of plasma proteins, and hormonal status (6). The majority of previous studies showed no clinically significant impact of older age on the clearance of docetaxel (3,4,7). However, a recent large meta-analysis revealed that patients with metastatic castration-resistant prostate cancer (mCRPC) had an almost two-fold lower systemic exposure compared to patients with other solid tumor types (8). Yet, data regarding docetaxel pharmacokinetic (PK) differences between mCRPC patients and patients with metastatic hormone-sensitive prostate cancer (mHSPC) are conflicting (9,10). In daily clinical practice, many elderly patients treated with docetaxel are diagnosed with prostate cancer, whereas the majority of younger patients have other solid tumors such as breast cancer. Thus, the net impact of older age on docetaxel PK may be masked by indication. This study was designed to assess the impact of older age on docetaxel PK in patients treated with docetaxel in the real-life setting, and taking into account any contributing effect of prostate cancer.

METHODS

Data Collection

Elderly patients aged 70 years or older who received docetaxel intravenously at the Netherlands Cancer Institute (NKI; Amsterdam, the Netherlands) or the Radboud University Medical Center (Radboud UMC; Nijmegen, the Netherlands) between September 2012 and September 2018 were eligible for study inclusion. If written informed consent was given, pharmacokinetic samples were withdrawn during one random docetaxel treatment cycle. A flexible pharmacokinetic (PK) sampling scheme was used, with the first sample drawn at the end of infusion. The collection of a minimum of 1 and a maximum of 10 samples per patient was allowed. Docetaxel PK samples were analyzed using a previously developed analysis method using high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS), with a validated concentration range of 0.5 to 500 ng/mL (11). All samples from prospectively included patients treated at the NKI and Radboud UMC were measured at the laboratory of the NKI. This study was approved by the institutional ethics committees and was carried out in accordance with ICH Guidelines for Good Clinical Practice (12).

PK data of these prospectively included elderly patients were combined with previously collected PK data from both elderly and younger patients (5). These retrospectively included patients were treated with intravenous docetaxel as part of a multicenter clinical trial. Median age was 54 years, with only 8% of patients aged 70 years or older. PK data from 5 out of 92 patients in this study cohort were missing in the archived dataset and appeared to be missing at random, and could not reliably be obtained due to data anonymization. Detailed information on study design and patient characteristics was described by Bosch *et al.* (5).

In this study, mCRPC was defined as a combination of castrate serum levels of testosterone (<50 ng/dL) and progressive disease defined as biochemical and/or radiological progression according to the European Association of Urology guidelines (13). Patients were considered to have mHSPC if they had non-castration-resistant metastatic prostate cancer with an indication for upfront docetaxel treatment, according to standard clinical care recommendations (14).

Population Pharmacokinetic Model

Docetaxel concentration-time data were described by a previously developed 3-compartment model with linear distribution and elimination. Here, a proportional model was used to assess interindividual variability (IIV) and residual error. Previously, multiple covariates have been associated with docetaxel clearance, of which hepatic impairment, albumin, AAG, and age were included in the validated full-covariate model by Bruno *et al.* (3). AAG was not routinely measured in daily clinical practice, and was not available for any of the prospectively included patients in our cohort. Therefore, this covariate was removed from the final covariate model. Recently, a meta-analysis has shown that mCRPC patients have about twice-lower systemic exposure compared to patients with other solid tumors (8). To date, the limited available data on PK differences between mCRPC and mHSPC patients are contradictory (9,10). Hence, the indication prostate cancer was added as a covariate affecting docetaxel clearance. Hereto, we categorized patients into three indication groups, namely mCRPC, mHSPC, and other solid tumors. This resulted in the following equation, adjusted from Bruno *et al.*, describing the relationship between clearance and covariates:

$$CL = BSA*(\Theta_1 + \Theta_2 ALB + \Theta_3 AGE)*(1-\Theta_4 HEP)*IND \quad (1)$$

With CL representing the individual clearance of docetaxel, BSA being the body surface area, Θ_1 representing the typical population value for clearance, Θ_2 representing the estimated influence of the covariate albumin (ALB), Θ_3 representing the estimated influence of age as a continuous variable (AGE), Θ_4 representing the estimated influence of hepatic impairment (HEP) defined as aspartate aminotransferase >60 IU/L and alkaline phosphatase >300 IU/L, and IND representing indication, being the parameter estimate Θ_5 for mCRPC patients, Θ_6 for mHSPC patients, and 1 for patients with other solid tumors. The continuous covariates BSA,

ALB, and AGE were centered on the median study population value, in order for clearance to represent clearance of a typical patient. If covariate data were missing, a separate covariate factor was added to the model for the missing part, to preclude bias from missing covariates.

Influence of Older Age

In the previously validated full-covariate model, age was included as a minor but significant covariate affecting docetaxel clearance (4). In the current dataset, including elderly patients treated in the real-life setting, the impact of older age was assessed using the above-formulated Eq. 1 with and without inclusion of the covariate age. Age was evaluated as a continuous variable, as depicted above, and as a dichotomous variable with the cohort divided into a group of patients aged ≥70 years and an age group of <70 years old. The impact of age on clearance was assessed by plausible parameter estimates, a drop in Objective Function Value (OFV) of >7.9, corresponding to a significance level of $p < 0.005$, goodness-of-fit (GOF) plots, visual predictive check (VPC) evaluation with $n = 1000$, and a clinically relevant impact of the effect of age on clearance. Parameter precision of the generated models was evaluated using sampling importance resampling (SIR) (15). To assess whether a potential impact of age on docetaxel PK might be driven by gender or performance status (PS), we additionally evaluated the effect of gender and PS, the latter depicted using the Eastern Cooperative Oncology Group (ECOG) scale. Data simulation using the final covariate model was performed to depict the impact of age on docetaxel clearance in 1000 patients. Separate simulations were executed for mCRPC patients, mHSPC patients, and for patients with other solid tumors with docetaxel administered at 75 mg/m^2 during a one-hour infusion.

Software

Non-linear mixed effects modeling was performed with NONMEM® (version 7.3.0, ICON Development Solutions, Ellicott City, MD, USA), Perl-speaks-NONMEM (version 4.4.8), and Pirana (version 2.9.8). The first order conditional estimation with interaction was used. Data management and graphical evaluation was performed using R (version 3.5.1).

RESULTS

This analysis included 157 patients, from whom 380 PK samples were available. Median age in the study database was 67 years, ranging from 31 to 87 years old. Elderly patients (≥70 years) represented 49% of the cohort, as depicted in Table I. Our study cohort comprised significantly more elderly male patients with prostate cancer *versus* younger female patients diagnosed with breast cancer. However, our study cohort also included elderly patients with other solid tumors and younger patients with prostate cancer. Furthermore, BSA was marginally but statistically significantly higher in elderly patients, whereas other baseline covariate values were comparable between elderly and their younger counterparts. The cohort included 72 patients with prostate cancer, comprised of 62 mCRPC patients and 10 mHSPC patients receiving upfront docetaxel treatment. Indication was evaluated as a covariate, categorized into three indication groups, namely mCRPC patients, mHSPC patients, and patients with other solid tumors. PK sampling was allowed during a random treatment cycle and was performed during the first to fifth cycle of upfront docetaxel treatment in mHSPC patients. Data on albumin and hepatic impairment was missing in 16% and 6% of patients, respectively. The covariates age, BSA, and indication contained no missing data.

The current study cohort contained a small number (4%) of patients with hepatic impairment and a relatively small range of albumin values and these covariate values were comparable between elderly and younger patients, as shown in Table I. Therefore, the previously reported covariate parameter estimates for hepatic impairment and albumin from the full-covariate model by Bruno *et al.* were used (0.334 and 0.225, respectively) (3). A separate fixed effect for missing hepatic impairment data could not be estimated in the current dataset. Because data on hepatic impairment were missing in only 6% of the patient cohort, we imputed the median values for missing ASAT and AF values. For albumin, a separate fixed effect was estimated for those patients with a missing albumin value.

We added the effect of mCRPC and mHSPC on clearance to the covariate model by Bruno *et al.* (4). Without inclusion of age, it appeared that mCRPC patients had a 10% lower docetaxel clearance than patients with other solid tumors, as depicted in Table II. Inclusion of age as a continuous variable into the model showed that age significantly affected docetaxel clearance ($p < 0.005$). For a typical patient with all covariates set to the population median values, a 10-year and 20-year increase of age led to a 17 and 34% lower docetaxel clearance, respectively. However, the inclusion of the covariate age led to a decrease in IIV of clearance of only 2%. Moreover, with the inclusion of age, docetaxel clearance was 20% higher in mCRPC patients and 51% higher in mHSPC patients as compared to patients with other solid tumors. GOF plots and the VPC results of this covariate model including age as a continuous variable are depicted in Figs. 1 and 2, respectively. The VPC results concern an interpercentile range of 80%, given the relative small number of observations. The results from this covariate model are also presented as a boxplot in Fig. 3, showing the estimated docetaxel clearance of elderly and younger patients (≥70 years *versus* <70 years) per indication group. Data simulations of this covariate model

Table I Baseline Patients' Characteristics

Parameter	Total cohort	≥70 years	<70 years	*P* value
Number of patients, n (%)	157 (100)	77 (49)	80 (51)	
Age (y), median [range]	67 [31-87]	74 [70-87]	51 [31-67]	
Dose (mg/m^2), median [range]	75 [15-102]	75 [25-100]	75 [15-102]	0.03
Infusion time (h), median [range]	1.1 [0.9-4]	1.0 [0.9-4]	1.1 [1.0-3.5]	<0.001
No. of samples (n)	379	158	221	
Per patient, median [range]	2 [1-15]	2 [1-15]	2 [1-15]	0.05
Sampling time (h), median [range]	1.8 [0.9-48.1]	1.3 [0.9-47.9]	6 [1.1-48.1]	<0.001
Female n (%)	73 (46)	6 (4)	67 (84)	<0.001
Indication, n (%)[#]				
mCRPC	62 (39)	54 (70)	8 (10)	<0.001
mHSPC	10 (6)	10 (13)	0	
Breast	61 (39)	3 (4)	58 (73)	
Lung	8 (5)	4 (5)	4 (5)	
Bladder	6 (4)	5 (6)	1 (1)	
Other	9 (6)	1 (1)	8 (10)	
Unknown	1 (1)	0	1 (1)	
BSA (m^2), median [IQR]	1.9 [1.4-2.3]	2.0 [1.5-2.3]	1.8 [1.4-2.2]	<0.001
Performance status	1 [0-2]	1 [0-2]	1 [0-2]	
0	31	17	14	
1	64	44	20	0.43
2	15	9	6	
Unknown	47	7	40	
Albumin (g/L), median [IQR]	42 [24-52]	42 [27-49]	43 [24-52]	0.31
Hepatic impairment, n (%)	6 (4)	2 (3)	4 (5)	0.44

[#] Total does not add up to 100% due to rounding

BSA body surface area, *h* hours, *IQR* Interquartile range 25th-75th percentile, *m*^{2} squared meter, *mCRPC* patients with metastatic castration-resistant prostate cancer, *mg* milligrams, *mHSPC* patients with metastatic hormone-sensitive prostate cancer, *n* number of patients, *y* years

with docetaxel administered at 75 mg/m^2 in a one-hour infusion are presented in Fig. 4. Additionally, age was also evaluated as a dichotomous covariate, with the cohort divided into a group of elderly (≥70 years) and a group of younger patients (<70 years). With age handled as a dichotomous variable, elderly patients had a 44% lower clearance compared to their younger counterparts ($p < 0.005$), with a decrease in IIV of clearance of 5%. Inclusion of the covariates gender or PS into the model did not alter the relationship between age and docetaxel clearance.

DISCUSSION

In this population PK study, docetaxel clearance was significantly lower in elderly patients. The impact of age, either treated as a continuous or dichotomous variable, was considered clinically relevant with a decrease in clearance of 17% per 10-year increment of age and a 44% lower clearance in elderly patients (≥70 years), respectively. Our results supported the theory that the inverse relationship between age and docetaxel clearance may have been masked by indication in previous studies.

Docetaxel clearance has been shown to be higher in mCRPC patients than in patients with other solid tumors (8), which is supported by our findings, although the effect was less than found earlier (8). The mechanistic basis for the observed difference in docetaxel clearance by indication remains unclear. It has previously been suggested that the decrease in systemic exposure in castrated men may be ascribed to an increase in the hepatocellular uptake of docetaxel (9). This may be caused by an increase in the hepatic expression of rOat2, which regulates the transport of docetaxel into hepatocytes. Furthermore, this and other studies showed no castration-dependent change in hepatic CYP3A4 activity that may explain differences in docetaxel PK (9,16).

In previous docetaxel PK studies, the impact of age appeared minor and was not considered to have clinical

Table II Population Pharmacokinetic Parameters of Docetaxel of the Covariate Model Generated Without and with Inclusion of the Continuous Variable Age

Parameter (unit)	Covariate model - AGE		Covariate model + AGE	
	Estimate	95% CI	Estimate	95% CI
CL (L/h)	53	47 - 59	44	40 - 50
V_1 (L)	13	11 - 15	12	10 - 14
V_2 (L)	9.8	4.5 - 17	9.9	4.9 - 16
V_3 (L)	257	204 - 359	261	213 - 353
Q_2 (L/h)	5.4	4.0 - 7.1	5.5	4.1 - 7.1
Q_3 (L/h)	14	11 - 17	14	11 - 17
AGE on CL	NA	NA	−0.755	−1.09 - -0.420
ALB on CL	0.225	Fixed	0.225	Fixed
HEP on CL	0.334	Fixed	0.334	Fixed
mCRPC on CL	0.90	0.77 - 1.06	1.20	1.01 - 1.43
mHSPC on CL	1.17	0.87 - 1.54	1.51	1.13 - 2.07
Interindividual variability				
CL (%)	45	39 - 53	43	36 - 50
V_1 (%)	22	10 - 31	21	9 - 30
V_3 (%)	33	15 - 55	36	14 - 55
Q_3 (%)	36	17 - 47	36	18 - 53
Residual variability				
σ_{prop}(%)	39	34 - 42	38	34 - 42

AGE age treated as a continuous variable, *ALB* albumin, *CL* docetaxel clearance, *HEP* hepatic impairment, defined as aspartate aminotransferase >60 IU/L and alkaline phosphatase >300 IU/L, *mCRPC* patients with metastatic castration-resistant prostate cancer, *mHSPC* patients with metastatic hormone-sensitive prostate cancer, *NA* not available/not applicable, $Q_{2\text{-}3}$ intercompartmental clearance between the central and either the second or the third peripheral compartment,respectively, *95% CI* 95% confidence interval from the Sampling Importance Resampling analysis, σ_{prop} proportional residual error, $V_{1\text{-}3}$ volume of the central, second peripheral and third peripheral compartment, respectively

relevance (4,17–22). Some of these studies included elderly patients with mCRPC, but the effect of mCRPC on docetaxel clearance was not considered (18–20). In the real-life setting, however, many elderly patients treated with docetaxel are diagnosed with prostate cancer. To our knowledge, our study is the first to jointly evaluate the effect of age and either mCRPC or mHSPC on docetaxel clearance.

Based on significantly improved survival shown in recent studies, docetaxel treatment may now be administered at the beginning of androgen deprivation therapy (ADT) to mHSPC patients (14,23). But to date, there is no conclusive data regarding a potential difference in docetaxel PK between patients with mCRPC and those with mHSPC. A study by Franke *et al.* showed a twofold higher docetaxel exposure in mHSPC patients compared to mCRPC patients ($n = 10$ and $n = 20$, respectively) (9). This study is balanced by a recent study by Belderbos *et al.*, showing no significant difference in exposure between mHSPC and mCRPC patients ($n = 11$ and $n = 7$, respectively) (10). Our study results are in line with the latter study, indicating that mHSPC patients do not have lower docetaxel clearance than patients with mCRPC. It should be noted that the study by Franke and colleagues evaluated blood samples collected during the first docetaxel treatment cycle. Instead, in the study by Belderbos *et al.* and in the current study, PK samples were drawn during later treatment cycles. By design, PK sampling in this study was allowed in a random docetaxel treatment cycle. As a consequence, samples were drawn from mHSPC patients who received up to five treatment cycles of docetaxel concomitantly administered with ADT. These differing lengths of testosterone suppression may partly explain the observed differences in exposure between these studies. Our data suggest that docetaxel PK differences may be driven by hormonal changes that occur in the early phase of ADT treatment, such as a drop in testosterone levels. One should also bear in mind that these studies, including the current study, enrolled a small number of mHSPC patients. Multiple studies reported a higher incidence of docetaxel-related neutropenia in mHSPC patients than mCRPC patients (8,9,24). It is unclear whether this may be driven by higher docetaxel exposure at the start of upfront docetaxel treatment or may be owing to a higher sensitivity to toxicity in mHSPC patients. Regardless of the impact of mCRPC and mHSPC on docetaxel clearance, this study showed that older age was a significant determinant of lower docetaxel clearance.

Although the magnitude of effect of older age on docetaxel clearance appeared to have clinical relevance, this only led to a minor decrease in IIV on clearance of docetaxel. Docetaxel shows large interpatient variability, which remains largely unexplained (2). Multiple previous studies showed that this variability may partly be explained by various covariates, including BSA, hepatic impairment, plasma proteins, age, hormonal status, and Cytochrome P-450 (CYP) activity (25–28). Measurements of AAG and CYP activity are generally not implemented in routine clinical practice, which was the case for all of the prospectively enrolled patients in our cohort. As these covariate data are generally not available for treating physicians during treatment decision-making, AAG and CYP activity were not considered in our covariate analysis. In previous studies, the clinical impact of AAG appeared minor and did not reach significance in some studies (4,27,28). It should be kept in mind however, that plasma proteins, such as AAG and albumin, may decline with increasing age (1,2). Although this age-related decline was not observed for albumin in our cohort, a comparison of AAG levels between elderly and younger patients could not be made in our cohort. For CYP3A4, the main docetaxel-metabolizing enzyme, no clinically relevant decline in activity in elderly patients has been suggested in studies using the validated probe midazolam (26,29). Therefore, it was not expected that AAG or CYP3A4 activity might thwart our findings. One may claim

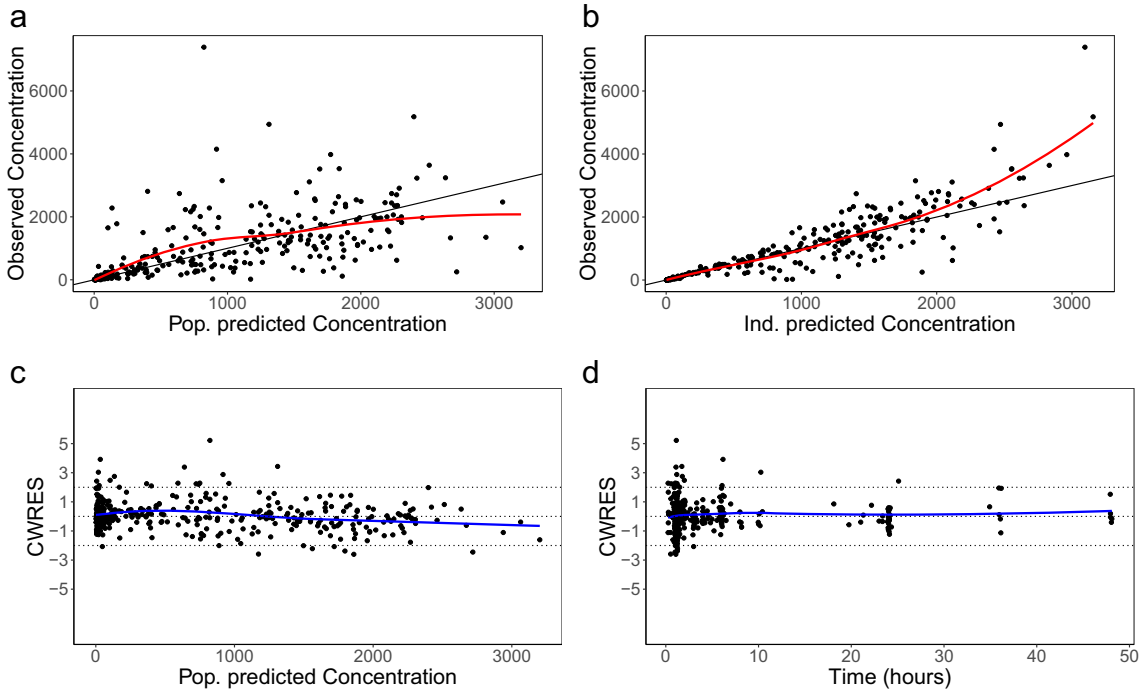

Fig. 1 Goodness-of-fit plots of the full-covariate model including age with (**a**) observed docetaxel concentrations *versus* population predictions of docetaxel concentrations, (**b**) observed docetaxel concentrations *versus* individual Bayesian predictions of docetaxel concentrations, (**c**) Conditional Weighted Residual Error (CWRES) *versus* population predictions of docetaxel concentrations, and (**d**) CWRES *versus* time after dose.

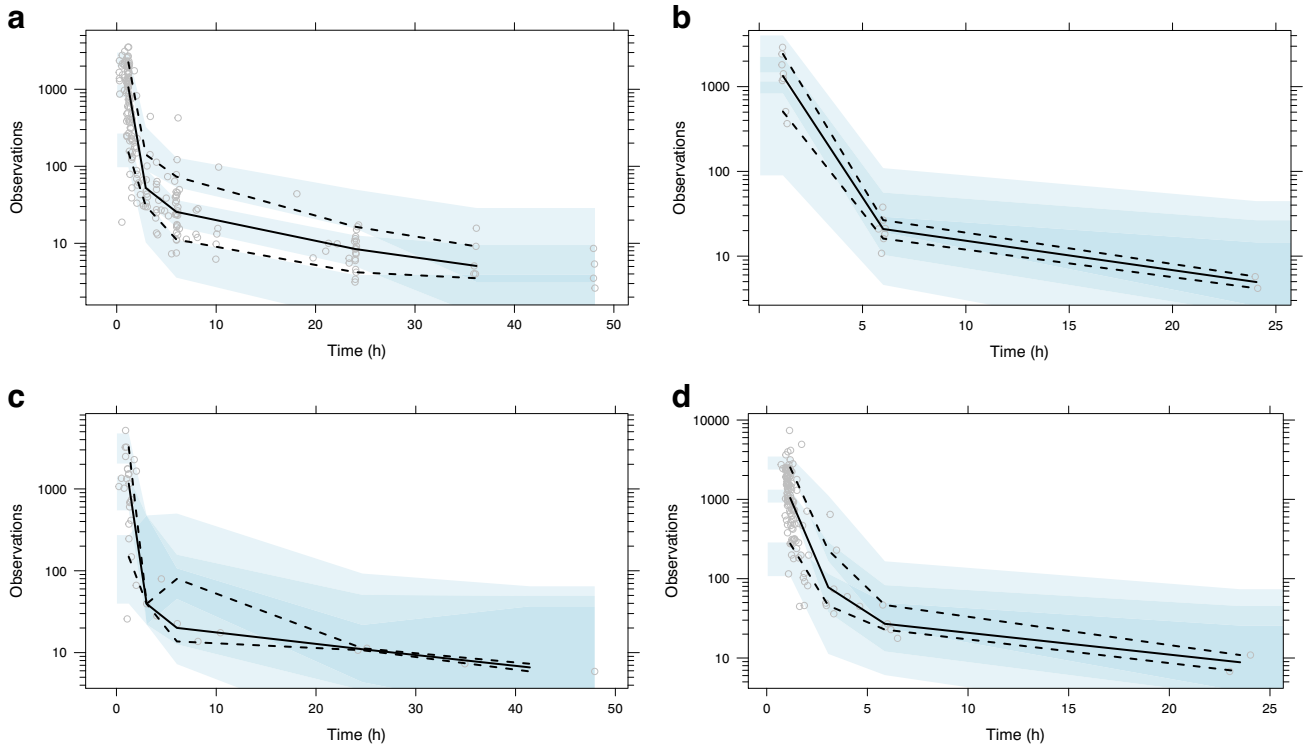

Fig. 2 Visual Predictive Check with $n = 1000$ of the covariate model including age as a continuous variable of (**a**) patients aged <70 years with other solid tumors, (**b**) patients aged <70 years with prostate cancer, (**c**) patients aged ≥70 years with other solid tumors, and (**d**) patients aged ≥70 years with prostate cancer. Data concern log-transformed docetaxel plasma concentrations, with the dots representing the observed concentrations, the solid line representing observed median concentrations, and dashed lines representing the 80% prediction intervals. The confidence intervals for the median and prediction intervals are shown as blue shaded areas.

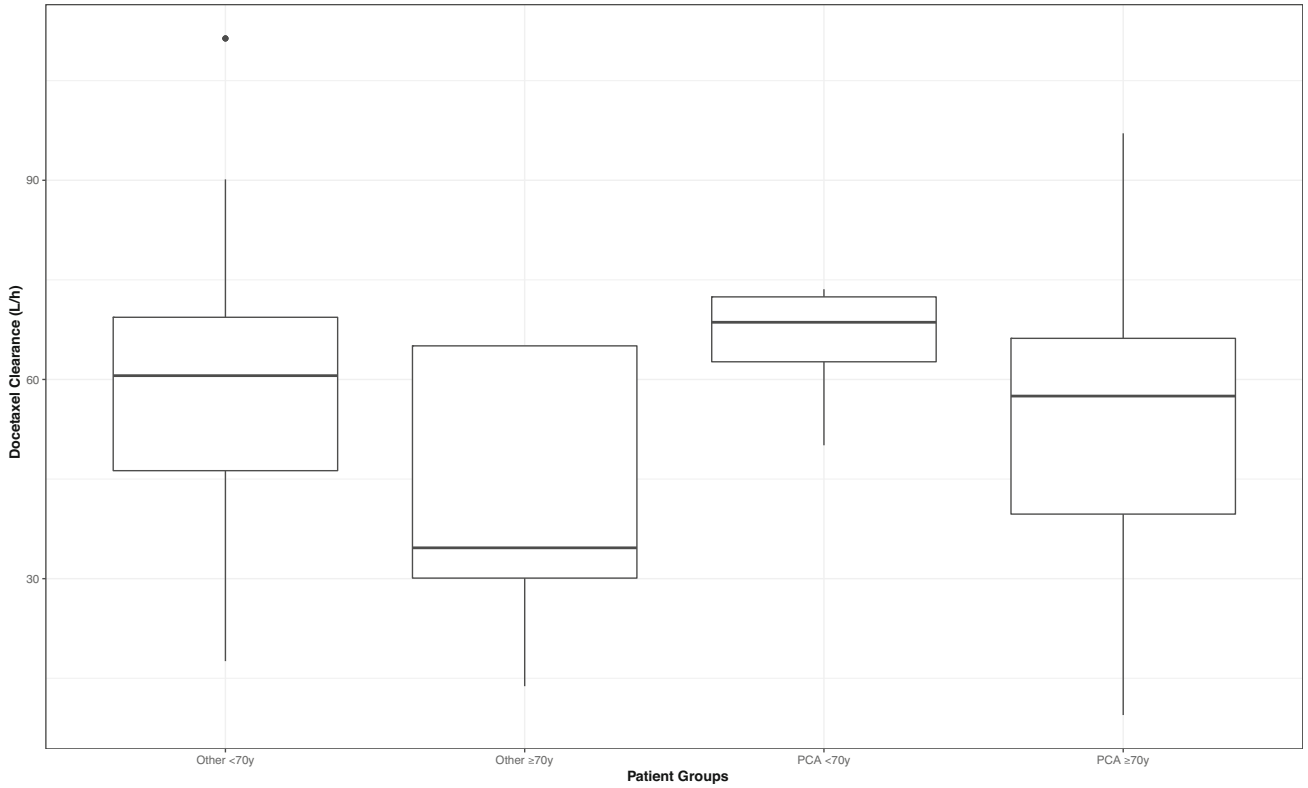

Fig. 3 Boxplot of the covariate model including age as a continuous variable, showing the estimated docetaxel clearance in younger (<70 years) and elderly patients (≥70 years) with other solid tumors (other) and with prostate cancer (PCA), respectively.

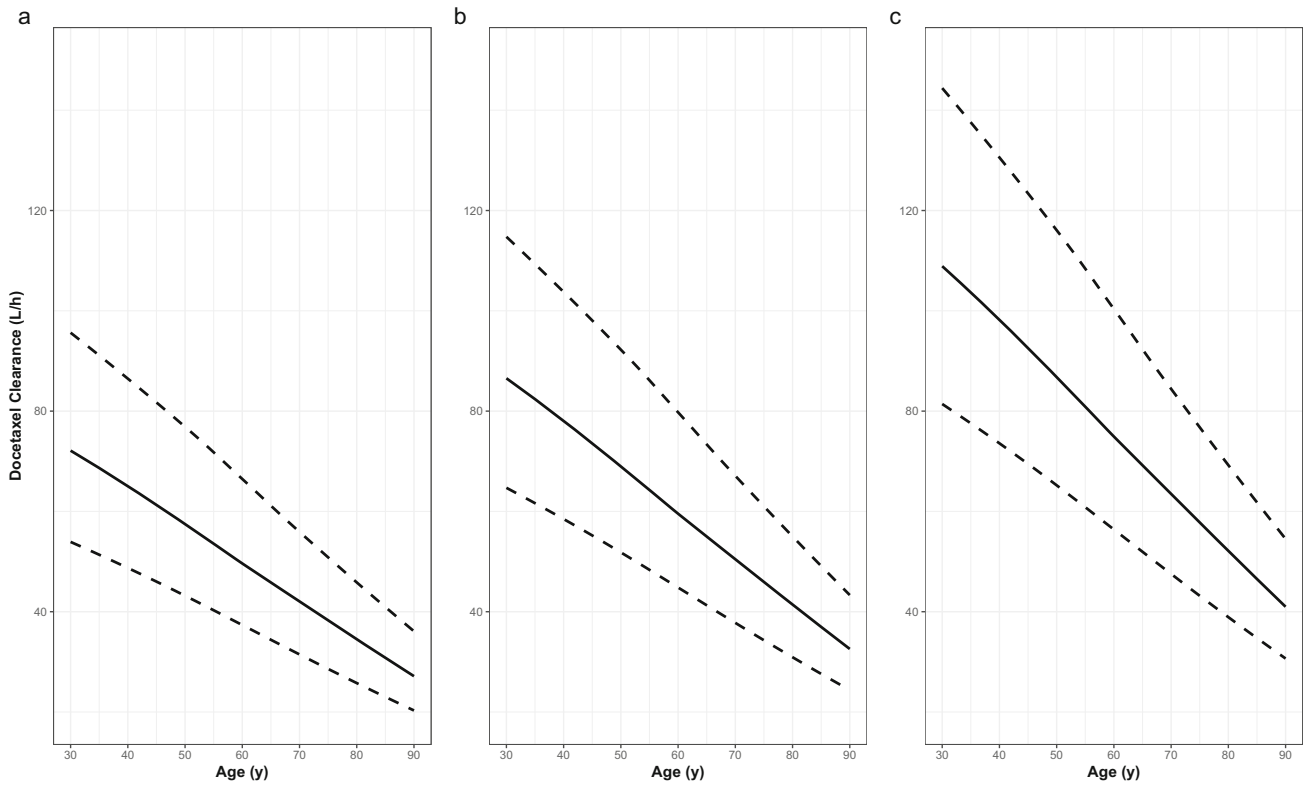

Fig. 4 Simulated effect of age on docetaxel clearance (**a**) in patients with solid tumors, excepting prostate cancer, (**b**) in mCRPC patients, and (**c**) in mHSPC patients with docetaxel administered at 75 mg/m^2 in a one-hour infusion.

that the impact of older age may be influenced by gender or PS, but neither covariate altered the relationship between age and docetaxel clearance in our analysis.

The observed age-related difference in docetaxel PK may at least partly explain the previously reported higher incidence of docetaxel-induced toxicity in elderly patients (17,19,20,30). Pivotal trial data on first-line docetaxel in mHSPC patients raised concern regarding neutropenia and neutropenia-related complications (24). Due to docetaxel-related deaths in the first large upfront docetaxel trial, the data monitoring committee recommended treatment with granulocyte colony-stimulating factor (31). Although less toxic docetaxel treatment regimens were assessed in elderly and in frail elderly patients (32), including weekly administered docetaxel, these regimens showed impaired treatment efficacy (2,33). In a retrospective study, 50% of the oldest patient cohort (≥75 years) was started on a reduced docetaxel dose *versus* only 12% of patients aged <65 years. This resulted in a significantly lower incidence of severe toxicity in the oldest patients, but was pursued by a lower overall survival as compared to their younger counterparts (34). To achieve maximal dose intensity and ultimately optimize treatment outcome in elderly patients, mandatory use of prophylactic granulocyte colony-stimulating factor may be necessary. On the other hand, with a lower systemic exposure in younger patients together with a relatively low incidence of hematological toxicity in younger mCRPC patients (35), one may claim that younger patients with mCRPC may benefit from higher docetaxel doses. Although this appears to be a promising approach, confirmation by a prospectively designed controlled trial is warranted.

In conclusion, our study showed that age significantly and independently affected docetaxel clearance. Elderly patients had significantly lower docetaxel clearance, with a 17% decrease in docetaxel clearance per 10-year increase of age. In our cohort, mCRPC and mHSPC patients both had higher clearance than patients with other solid tumors.

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