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RESEARCH PAPER

Impact of Older Age on the Exposure of Paclitaxel: a Population Pharmacokinetic Study

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ABSTRACT

Purpose Limited available data suggest that older patients are more prone to develop paclitaxel-induced toxicity than their younger peers. It remains unclear whether this is related to age-dependent pharmacokinetics (PK) of paclitaxel. Primary objective of this study was to determine the influence of older age on the PK of paclitaxel.

Methods PK data of patients aged ≥70 years who received paclitaxel intravenously at the Netherlands Cancer Institute (NKI) and the Radboud University Medical Center between September 2012 and May 2017 were collected. These prospectively collected data were pooled with previously published databases from multiple clinical trials conducted at the NKI and Erasmus MC Cancer Institute. A previously developed 3-compartment population PK model with saturable distribution and elimination was used to describe paclitaxel plasma concentration-time data. Hereafter, influence of age on paclitaxel PK was assessed in a previously established full covariate model.

Results In total, paclitaxel PK data from 684 patients were available, consisting of 166 patients ≥70 years (24%). Median age of the cohort was 61 years (range 18 to 84 years). The impact of age, either treated as a continuous or dichotomous covariate (<70 *versus* ≥70 years), on the elimination of paclitaxel was only marginal but statistically significant (both $p < 0.001$ with no clinically relevant decrease in interindividual variability). For a typical patient, maximal elimination capacity decreased by only 5% for a 10-year increment of age.

Conclusion In this extensive multi-center dataset, which included a considerable number of older patients, older age had no clinically relevant impact on paclitaxel PK.

KEY WORDS age differences · older patients · paclitaxel · pharmacokinetics

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ABBREVIATIONS

A_{1-3}	Amount of paclitaxel in first-third compartment
C_1	log-transformed concentration of paclitaxel in central compartment
EMC	Erasmus Medical Center Cancer Institute
HPLC-MS/MS	High-performance liquid chromatography coupled with tandem mass spectrometry
K	rate constant of the distribution between compartments
KM_{EL}	plasma concentration at half VM_{EL}
KM_{TR}	plasma concentration at half VM_{TR}
NKI	Netherlands Cancer Institute

PK	Pharmacokinetics
Radboud UMC	Radboud University Medical Center
VM_{EL}	maximal elimination rate
VM_{TR}	maximal transport rate from the central to the first peripheral compartment

INTRODUCTION

Cancer predominantly occurs in older adults (1). The proportion of older adults worldwide is increasing, and anti-cancer treatment is ever more used in older patients. However, the elderly subpopulation was markedly underrepresented in most clinical trials (2–5). Treatment safety and efficacy may differ between older and younger patients, due to a progressive reduction in organ functions and comorbidities (6). Therefore, clinical trial results from younger patients cannot plainly be extrapolated to older patients treated in routine clinical practice. Paclitaxel is a potentially highly toxic chemotherapeutic agent frequently used in daily practice to treat older patients with various cancer types including ovarian cancer, lung cancer, breast cancer, and esophageal cancer. As with older age the fraction of body fat generally increases and hepatic functions may be diminished (7,8), we hypothesized that the pharmacokinetics (PK) of the lipophilic drug paclitaxel may be altered in elderly patients. Although data are limited and results are conflicting, most studies suggest that older patients have an increased risk of developing paclitaxel-induced neutropenia compared to their younger peers (9–11). A potential PK basis for these findings has not consistently been established in clinical practice.

In previous studies conducted with data from the Netherlands Cancer Institute (NKI; Amsterdam, the Netherlands) we showed a small but significant effect of age on paclitaxel PK (12,13). However, the total fraction of older patients (≥70 years) in the final pooled analysis from multiple clinical trials was only 6.7% (13). This finding was in line with analyses from clinical trials conducted at the Erasmus Medical Center Cancer Institute (EMC; Rotterdam, the Netherlands), showing no effect of aging on paclitaxel PK (14–16). This EMC database consisted of different clinical trials including patients treated with paclitaxel, including 18% of patients being 70 years of age or older.

The aim of the current study was to evaluate whether older patients have an increased exposure to paclitaxel. Therefore, the aforementioned previous databases from the NKI and EMC were combined and enriched with a prospective PK dataset collected in an unselected group of patients aged 70 years or older who were treated with paclitaxel intravenously in routine clinical practice.

METHODS

Prospective Data

Patients of 70 years or older who received an intravenous infusion of paclitaxel at the NKI or the Radboud University Medical Centre (Radboud UMC; Nijmegen, the Netherlands) were included in the study if written informed consent was given. The inclusion period was from September 2012 to May 2017, and for PK purposes, additional blood samples were taken according to a flexible sampling scheme, with the first sample collected at the end of infusion. The number of withdrawn blood samples was based on each patient's availability with a minimum of 1 and a maximum of 10 samples per patient. PK sampling was allowed during any treatment cycle. Paclitaxel plasma concentrations from both hospitals were determined at the NKI using a previously validated high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) detection method, with a validated range of 0.5–500 ng/mL (inter-assay accuracy and precision both <10%) (17).

All paclitaxel containing regimes were administered according to standard procedures of the participating study centers, using fixed infusion times, dose reduction guidelines, and premedication. The prospective part of this study was approved by the institutional ethics committees and was carried out in accordance with ICH Guidelines for Good Clinical Practice (18).

Retrospective Data

Data collected in the prospective study were combined with retrospective data from previous clinical trials conducted at the NKI and EMC. Twelve patients from the NKI retrospective cohort who were treated with 24 h infusions of paclitaxel were excluded from the current analysis. This resulted in a total of 595 patients who were included in previous clinical trials, including 77 (13%) patients aged 70 years or older. These populations were described in detail in previously published articles (12–16).

Population Pharmacokinetic Model

A previously developed 3-compartment population PK model with saturable distribution and saturable elimination (13) was used to describe paclitaxel plasma concentration-time data, with natural logarithmic transformation of the plasma concentrations of paclitaxel, using the following differential equations:

$$\frac{dA_1}{dt} = -\frac{C_1 * VM_{EL}}{(KM_{EL} + C_1)} + K_{21} * A_2 - \frac{C_1 * VM_{TR}}{(KM_{TR} + C_1)} + K_{31} * A_3 - K_{13} * A_1 \quad (1)$$

$$\frac{dA_2}{dt} = \frac{C_1 * VM_{TR}}{(KM_{TR} + C_1)} - K_{21} * A_2 \quad (2)$$

$$\frac{dA_3}{dt} = K_{13} * A_1 - K_{31} * A_3 \quad (3)$$

where A_1, A_2, and A_3 represent the amount of paclitaxel in central, first peripheral, and second peripheral compartment, respectively. C_1 represents the log-transformed concentration of paclitaxel in central compartment, VM_{EL} represents the maximal elimination rate, KM_{EL} is the plasma concentration at half VM_{EL}, VM_{TR} represents the maximal transport rate from the central to the first peripheral compartment, KM_{TR} is the plasma concentration at half VM_{TR}, and K_{21}, K_{31}, and K_{13} represent the rate constant of the distribution between the central and first and second peripheral compartment, respectively.

Random Effects Model

Characterization of interindividual variability (IIV) on VM_{EL}, VM_{TR}, KM_{TR}, Q and V_3, and inter-occasion variability (IOV) on V_1 and VM_{EL} was performed using exponential error models. The magnitude of IIV and IOV was expressed as percent coefficient of variation. In the previously published model (13), the residual error model was characterized using a proportional error model. A separate proportional error was evaluated for each included cohort, i.e. the retrospective NKI cohort, the retrospective EMC cohort, and the prospective cohort, given that different analytical assays had been used. In one of the retrospective databases, observations below the quantification limit of the assay (BQL) were discarded. It could not be retrieved from which patients data were discarded. Therefore, regular methods for handling BQL observations could not be used. However, the sensitivity of the assays was sufficient to quantify all observations at least until 24 h after end of infusion. To mitigate potential (unknown) bias caused by these hidden BQL data in this cohort, only in this cohort an additive error was added. Hence, we considered a proportional error for each cohort, and for one cohort an additive error was estimated together with the proportional error, using the following equation (19):

$$\ln(C_{ij,obs}) = \ln(C_{ij,pred}) + \sqrt{\varepsilon_{ij,prop}^2 + \frac{\varepsilon_{ij,add}^2}{C_{ij,pred}^2}} \quad (4)$$

where $C_{ij,obs}$ represents the observed concentration for the ith individual and the jth observations, $C_{ij,pred}$ represents the individual predicted concentration for the ith individual and the jth observations, and $\varepsilon_{ij,prop}$ and $\varepsilon_{ij,add}$ represent the proportional and additive error, respectively, distributed $N(0,\sigma^2)$, where σ^2 represents the population variance for the residual unexplained variability.

Evaluation of Age as a Covariate

The previously published model (13) already included age, gender, body surface area (BSA), and total bilirubin (BILI) as significant covariates on VM_{EL}, the primary PK parameter of interest. To evaluate the impact of older age on paclitaxel PK in the current enriched dataset, we evaluated the base model and covariate model without and with inclusion of the covariate age. Age was included both as a continuous and as a dichotomous variable, by dividing the population into two age groups, namely younger patients (<70 years) and older patients (≥70 years). All continuous variables were centered on their median value of the study population, in order for population parameter estimates to represent those of a typical patient. For evaluation of categorical covariates, e.g. gender, on the maximal elimination rate (VM_{EL}) the following equation was used:

$$VM_{EL} = \Theta_1 * \Theta_2^{GENDER} * exp^{\eta i} \quad (5)$$

where Θ_1 represents the maximal elimination rate in females, Θ_2 represents the maximal elimination rate in males (GENDER = 1), and ηi represents the interindividual error. This equation was also used to evaluate the impact of age as a dichotomous variable, divided into two age groups. For the continuous variables age, BSA, and bilirubin, respectively, the following equation was used:

$$VM_{EL} = \Theta_1 * \left(\frac{COV}{COV_{median}}\right)^{\Theta_2} * exp^{\eta i} \quad (6)$$

where Θ_1 represents the typical population value for the maximal elimination rate, COV represents the continuous covariates age, BSA, and bilirubin, respectively, centered to their population median value of the study population, Θ_2 represents the exponential factor per continuous covariate to describe the correlation with the maximal elimination rate, and ηi represents the interindividual error.

For covariates for which there were missing values, a separate estimate for missing values was added to the model. The influence of older age on VM_{EL} was evaluated by statistical significance using the likelihood ratio test with a p value of <0.005 (corresponding to a decrease in objective function (dOFV) of >7.9), a clinically relevant decrease in IIV on VM_{EL}, goodness-of-fit (GOF) diagnostics, visual predictive check (VPC) evaluation with $n = 1000$, and plausibility of parameter estimates. To evaluate whether the impact of older age on paclitaxel PK could be explained by performance status (PS), the impact of this covariate was evaluated in a model including age. PS was defined using the Eastern Cooperative Oncology Group (ECOG) scale. If the Karnofsky scale was documented in a patient's medical record, the ECOG PS was calculated using the proposed conversion table by Ma *et al.* (20). Simulations with the final model were performed to

evaluate the impact of age on the time-above-threshold-concentration of 0.05 μmol/L ($T_{C>0.05}$, depicted in hours). Hence, a population of $n = 1000$ was simulated separately for female and male patients, who all received paclitaxel 80 mg/m^2 in a 1-h infusion, with all other covariates in the final model set to their population median.

Software

Non-linear mixed effects modeling was performed using NONMEM® (version 7.3.0, ICON Development Solutions, Ellicott City, MD, USA) and Pearl-speaks-NONMEM (version 4.4.8). As estimation method the first order conditional estimation with interaction was used. Piraña® (version 2.9.2) was used as modeling environment and data management and visualization was performed using R (version 3.0.1). Furthermore, on rank sum test and Fisher's exact test, with a significance threshold of $P < 0.05$, were used to evaluate patients' characteristics.

RESULTS

In total, 5895 samples from 684 patients (range: 1–20 per patient per cycle) treated with intravenously administered paclitaxel were included in the population PK analysis, as depicted in Table I. The dataset contained 166 patients aged ≥70 years (24%), of whom 89 patients were prospectively included. Median age of the total cohort was 61 years, ranging from 18 to 84 years old. Median age of the group of older patients (≥70 years) was 73 years, whereas median age of younger patients (<70 years) was 57 years. Administered paclitaxel doses ranged from 38 to 290 mg/m^2, administered as an infusion in 1 to 5 h, with blood sampling up to 55.6 h after the start of paclitaxel infusion. Older patients received the 3-weekly paclitaxel scheme significantly less frequent than their younger peers (32% of older *versus* 67% of younger patients). After grouping patients receiving weekly paclitaxel administrations and those receiving 3-weekly administrations, no large age-related differences in paclitaxel administrations were observed. However, a small but significant difference in weekly-administered dose was observed between both age groups, with a difference in median value of 3 mg/m^2 and a difference in mean value of 8 mg/m^2. In older patients, the sampling time after paclitaxel administration was shorter with fewer samples per patient per cycle (3 in elderly *versus* 5 samples in younger patients), with a median sampling time of 3.1 h after start of infusion in the older patient group compared to 4.1 h in the younger patient group. Other baseline characteristics were comparable between both age groups, as shown in Table I. Baseline bilirubin was missing in 25% of patients and appeared to be randomly missing in the dataset. The covariates age, BSA, and gender contained no missing data.

In Fig. 1, actual measured paclitaxel plasma concentrations *versus* time are displayed per age group.

To evaluate the impact of older age on paclitaxel PK, age was introduced as a continuous covariate into the base model, as depicted in Table II. Addition of age to the base model proved to be borderline significant (dOFV = 9) with a decrease in IIV of VM_{EL} of around 1%.

Subsequently, the effect of age was also estimated in the covariate model including BSA, gender, and bilirubin. Introduction of age as a continuous variable proved to be significant (dOFV = 33), but the decrease in IIV of VM_{EL} was only 1.0%. GOF diagnostics of observed *versus* predicted log-transformed paclitaxel plasma concentrations and the VPC with $n = 1000$ of the covariate model including age as a continuous variable are shown in Figs. 2 and 3, respectively. For a typical male or female patient, with median values for BSA and bilirubin, a decrease in VM_{EL} of 5% was calculated for a 10-year increment from the median age, as shown in Fig. 4. The influence of age treated as a dichotomous variable (<70 years *versus* ≥70 years) was also significant (dOFV = 19) in the covariate model. In this dichotomous age model, VM_{EL} was 17% higher in younger patients than in older patients, with a median VM_{EL} of 30.8 μmol/h in younger and 36.0 μmol/h in older patients. The corresponding decrease in IIV of VM_{EL} was only 0.3%. Inclusion of performance status as covariate did not change the relationships between VM_{EL} and age. Simulations of female and male patients aged between 25 and 90 years old, receiving 80 mg/m^2 in a 1-h infusion, revealed that the influence of higher age on the $T_{c>0.05\mu M}$ was small, as depicted in Fig. 5. With a 10-year increment an increase of less than 10% was observed. For instance, the difference between a typical 70-year old and 80-year old female or male patient was 6%.

DISCUSSION

In this extensive dataset including a considerable number of elderly patients, older age had a marginal but nevertheless statistically significant impact on the maximal elimination capacity of paclitaxel. Given the considerable interindividual variability of paclitaxel PK and minimal effect of age on this unexplained variability, the minor drop of paclitaxel elimination capacity in elderly patients is not considered clinically relevant.

In the current study we used the 3-compartment model that was previously developed by Joerger *et al.* (13), and the dataset of Joerger *et al.* was also included in the current analysis. We performed extensive model evaluation to assess whether the added datasets were indeed adequately described by this previous model, e.g. including stratification on study cohort, and regimen. We could not identify major differences in model fit and for consistency have ultimately chosen to use the Joerger model to evaluate the influence of age on

Table I Baseline Patients' Characteristics

Parameter	Total cohort	Aged < 70 yrs	Aged ≥ 70 yrs	*p* value
Number of patients (n)	684	518	166	<0.001
Weekly regimen	282 (41)	169 (33)	113 (68)	
3-weekly regimen	402 (59)	349 (67)	53 (32)	
Age (y), med.[range]	61 [18–84]	57 [18–69]	73 [70–84]	
Paclitaxel dose (mg/m^2), med. [range]				
Weekly regimen	52 [38–103]	54 [44–103]	51 [38–101]	<0.001
3-weekly regimen	175 [88–290]	175 [95–290]	175 [88–225]	0.49
Infusion time (h), med. [range]				
Weekly regimen	1 [1–4]	1 [1–4]	1 [1–3]	0.05
3-weekly regimen	3 [1–5]	3 [1–5]	3 [1-4]	0.5
No. of samples (n)	5895	5216	679	0.003
Per patient per cycle, med. [range]	4 [1–20]	5 [2–20]	3 [1–19]	
Sampling time (h), med. [range]	4.0 [0.1–55.6]	4.1 [0.3–55.6]	3.1 [0.1–46.2]	<0.001
Female n, (%)	383 (56)	300 (58)	83 (50)	0.09
Indication, n (%)				0.051
Lung	147 (21.5)	133 (25.7)	14 (8.4)	
Gynaecological	235 (34.3)	209 (40.3)	26 (15.7)	
Breast	50 (7.3)	15 (2.9)	35 (21.1)	
Upper GI	194 (28.4)	119 (23.0)	75 (45.2)	
Urological	22 (3.2)	11 (2.1)	11 (6.6)	
Sarcoma	2 (0.3)	0	2 (1.2)	
Head/neck	13 (1.9)	12 (2.3)	1 (0.6)	
Unknown	21 (3.1)	19 (3.7)	2 (1.2)	
Hospital				<0.001
NKI	359 (52)	255 (49)	104 (63)	
EMC	321 (47)	263 (51)	58 (35)	
Radboud	4 (1)	0	4 (2)	
BSA (m^2) med.[IQR]	1.8 [1.7–2.0]	1.8 [1.7–2.0]	1.8 [1.7–2.0]	0.46
Performance Status, med.[range]	1 [0–3]	1 [0–3]	1 [0–3]	0.2
Albumin (g/L),med.[IQR]	41 [37–43]	41 [37–43]	41 [38–43]	0.25
Bilirubin, total (μmol/L), med.[IQR]	7 [5–9]	7 [5–9]	7 [5–9]	0.56

BSA = body surface area, Gynaecological = ovarian, endometrium, mullarian, cervix and vaginal cancer, h = hours, IQR = Interquartile range 25th–75th percentile, m^2 = squared meter, med. = median, mg = milligrams, n = number of patients, Upper GI = esophageal and cardia cancer, Urological = testis, bladder, prostate, and kidney cancer, y = years

paclitaxel PK. Results from the current study are in line with paclitaxel PK parameters reported in previous studies, especially considering paclitaxel's broadly reported large interindividual variability (12,13,15). Older patients received the 3-weekly schedule less frequently than their younger peers. However, no large differences were observed between older and younger patients receiving either 3-weekly or weekly paclitaxel administrations. Although a difference in weekly-administered paclitaxel median dose of 3 mg/m^2 between older and younger patients reached significance in this large cohort, the absolute difference was very small. All patients included in this analysis received paclitaxel administered as a short infusion, ranging from 1 to 5 h. A recent meta-analysis showed a non-linear paclitaxel PK profile after short infusions (≤6 h) (21). This meta-analysis also showed that infusions of >24 h followed linear PK which were not comparable to shorter infusions. With the introduction of corticosteroid and antihistamine premedication, the 24 h infusion schedule is rarely used in clinical practice today. Therefore, twelve patients from the NKI retrospective cohort who were treated with 24 h infusions of paclitaxel were excluded from the current analysis.

Previous studies have reported conflicting results regarding the impact of older age on paclitaxel PK, ranging from no effect of aging up to an approximately 20% lower total paclitaxel clearance in older patients compared to their younger counterparts (9,10,13,22,23). Our study clearly showed that there is no PK basis for the posed increased risk of developing paclitaxel-related neutropenia in older patients. Therefore, it is postulated that this difference can be ascribed to greater

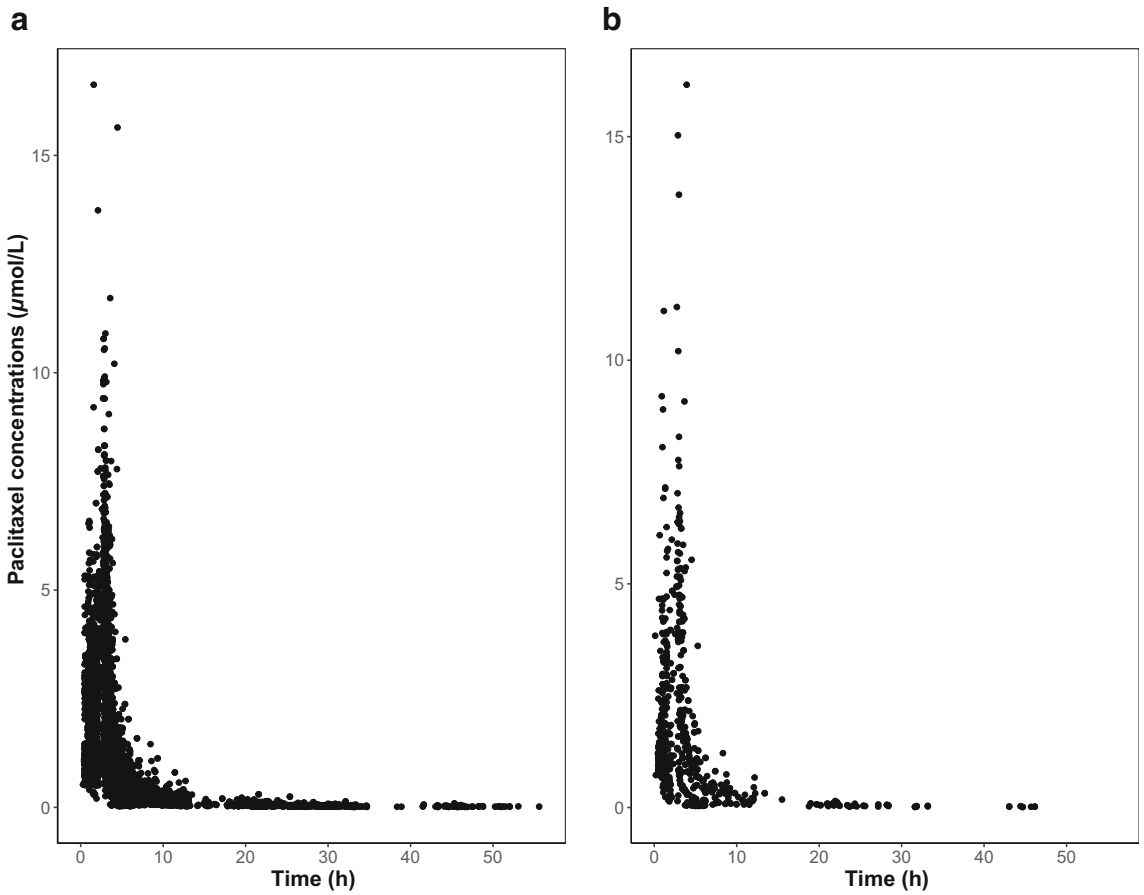

Fig. 1 Measured paclitaxel plasma concentration (μmol/L) versus time (hours) plots per age group, in (**a**) patients <70 years old, and in (**b**) patients aged 70 years or older.

treatment sensitivity, regardless of paclitaxel exposure, which may be due to a deprivation of bone marrow reserve or a reduced capacity for recovery from hematological stress in elderly patients (24).

One may be concerned that patients included in clinical trials do not reflect the typical older cancer patient treated in routine clinical practice, due to e.g. strict inclusion criteria for trial participants. The current analysis combined patients from multiple clinical trials with a prospectively included heterogeneous population of older patients selected to receive paclitaxel treatment in routine clinical practice. To enable inclusion of all previously collected paclitaxel PK data, the current study described total paclitaxel plasma concentrations. Although it is acknowledged that the free concentration might be more predictive of its effect than the total concentration, to our knowledge, this improved correlation has not adequately and prospectively been confirmed for paclitaxel (25). Paclitaxel has been shown to bind to serum albumin, but in the current study serum albumin values were comparable between older and younger patients, and its effect on paclitaxel PK appeared minor. To our knowledge, this study included the largest number of patients thus far to evaluate the effect of older age on paclitaxel exposure. Findings are in line with the majority of previous studies, showing a clinically negligible effect of older age on paclitaxel pharmacokinetics.

Time-above-threshold-concentration of 0.05 μmol/L ($T_{c>0.05\mu M}$) was shown to be related to paclitaxel treatment efficacy, neuropathy, and hematological toxicity (26–30). Preliminary data suggested that, after weekly-administered paclitaxel, $T_{c>0.05\mu M}$ was predictive of efficacy and neurotoxicity (14,26,27). In the current study, the majority of older patients received weekly-administered paclitaxel. For simulation purposes we used the commonly used weekly-administered dose of 80 mg/m^2. This may explain why our simulations resulted in lower $T_{c>0.05\mu M}$ compared to several previous studies (28–30), although it appeared to be in line with reported $T_{c>0.05\mu M}$ in multiple other studies including both weekly-administered and the 3-weekly paclitaxel regimen (15,16,26,27). Nonetheless, the marginal impact of older age on time-above-threshold-concentration of paclitaxel was statistically significant but was not considered to have clinical relevance.

In the current study, age was evaluated both as a continuous variable and as a dichotomous variable using a cut-off value of 70 years. By assessing age as a continuous variable no data were discarded thus providing the most informative analysis. Additionally, we dichotomized data to facilitate a

Table II Population Pharmacokinetic Parameters of Paclitaxel of the Base Model, Base Model Including Age, Covariate Model without Age, and Full Covariate Model Including Age

Parameter (unit)	Base model - AGE		Base model + AGE		Covariate model - AGE		Covariate model + AGE	
	Estimate	*RSE (%)*	*Estimate*	*RSE (%)*	*Estimate*	*RSE (%)*	*Estimate*	*RSE (%)*
VM_{EL} (μmol/h)	33.8	5	32.9	5	32.5	4	31.7	5
V_1 (L)	12.0	3	12.0	3	12.1	3	12.0	3
V_3 (L)	268	5	270	5	269	4	267	4
KM_{EL} (μmol/L)	0.44	7	0.43	7	0.45	7	0.46	7
VM_{TR} (μmol/h)	177	3	177	3	175	3	177	3
KM_{TR} (μmol/L)	1.61	6	1.59	6	1.63	6	1.63	6
K_{21} (h^{-1})	1.21	3	1.22	3	1.19	2	1.20	2
Q (L/h)	16.8	5	17.0	4	16.5	4	16.6	4
Age on VM_{EL}	NA	NA	−0.20	36	NA	NA	−0.31	17
BSA on VM_{EL}	NA	NA	NA	NA	1.39	9	1.41	8
Gender on VM_{EL}	NA	NA	NA	NA	1.11	3	1.12	3
Bilirubin on VM_{EL}	NA	NA	NA	NA	−0.16	15	−0.17	15
Interindividual variability								
VM_{EL} (%)	27.0	6	26.8	6	19.2	8	18.2	8
V_3 (%)	36.2	8	35.9	8	34.9	8	34.7	8
VM_{TR} (%)	26.7	6	26.7	6	26.6	6	26.7	6
KM_{TR} (%)	66.0	6	66.0	6	65.8	6	65.4	6
Q (%)	49.5	5	49.1	5	49.6	5	49.1	5
Inter-occasion variability								
V_1 (%)	49.2	3	49.2	3	49.1	3	49.2	3
VM_{EL} (%)	16.9	7	16.8	7	16.1	7	16.1	7
Residual variability								
σ_{add} (μM)	0.006	5	0.006	5	0.006	5	0.006	4
σ_{prop1}	0.141	1	0.140	1	0.141	1	0.141	1
σ_{prop2}	0.467	8	0.466	8	0.459	8	0.458	8
σ_{prop3}	0.290	2	0.291	2	0.289	2	0.291	2

AGE = age evaluated as a continuous variable, BSA = body surface area, K_{21} = rate constant of the distribution from the first peripheral compartment to the central compartment, KM_{EL} = plasma concentration at half VM_{EL}, KM_{TR} = plasma concentration at half VM_{TR}, NA = not available/not applicable, Q = intercompartmental clearance between the central and second peripheral compartment, RSE = relative standard error, σ_{add} = additive residual error, σ_{prop1} = proportional residual error of retrospective NKI cohort, σ_{prop2} = proportional residual error of retrospective EMC cohort, σ_{prop3} = proportional residual error of prospective cohort, V_1 = volume of the central compartment, V_3 = volume of the second peripheral compartment, VM_{EL} = maximal elimination rate, VM_{TR} = maximal transport rate from the central to the first peripheral compartment

more forward interpretation and presentation on the influence of older age on paclitaxel PK. The hereto applied cut-off value of 70 years was used because multiple studies have shown that organ functions may rapidly decline while chemotherapy-induced hematological toxicities tend to increase steeply after the age of 70 (24). By design, this study included various paclitaxel dose regimens administered in monotherapy or concomitantly with other chemotherapeutic agents. Because previous studies showed no influence on the PK of paclitaxel with co-administration of cisplatin (31–33), carboplatin (34,35), or doxorubicin (36), these per protocol administered combination treatments were not excluded from the current analysis. As part of clinical practice, concomitantly administered medication was strictly monitored to prevent possible drug-drug interactions. However, this was not a strict exclusion criterion of the current study. Prospectively included older patients in this cohort generally received paclitaxel treatment as part of outpatient care, which led to shorter sampling times in the older patient group. This may introduce potential bias, although full PK curves from older patients included in previous clinical trials were available. Besides, the flexible sampling scheme was implemented in order to lower barriers to enrollment of frail older patients in the dataset. Furthermore, both the retrospectively included datasets and the prospectively included observational cohort contained missing covariate data. Because our main objective was to evaluate the influence of older age on the elimination capacity of paclitaxel, thorough evaluation of other covariates and

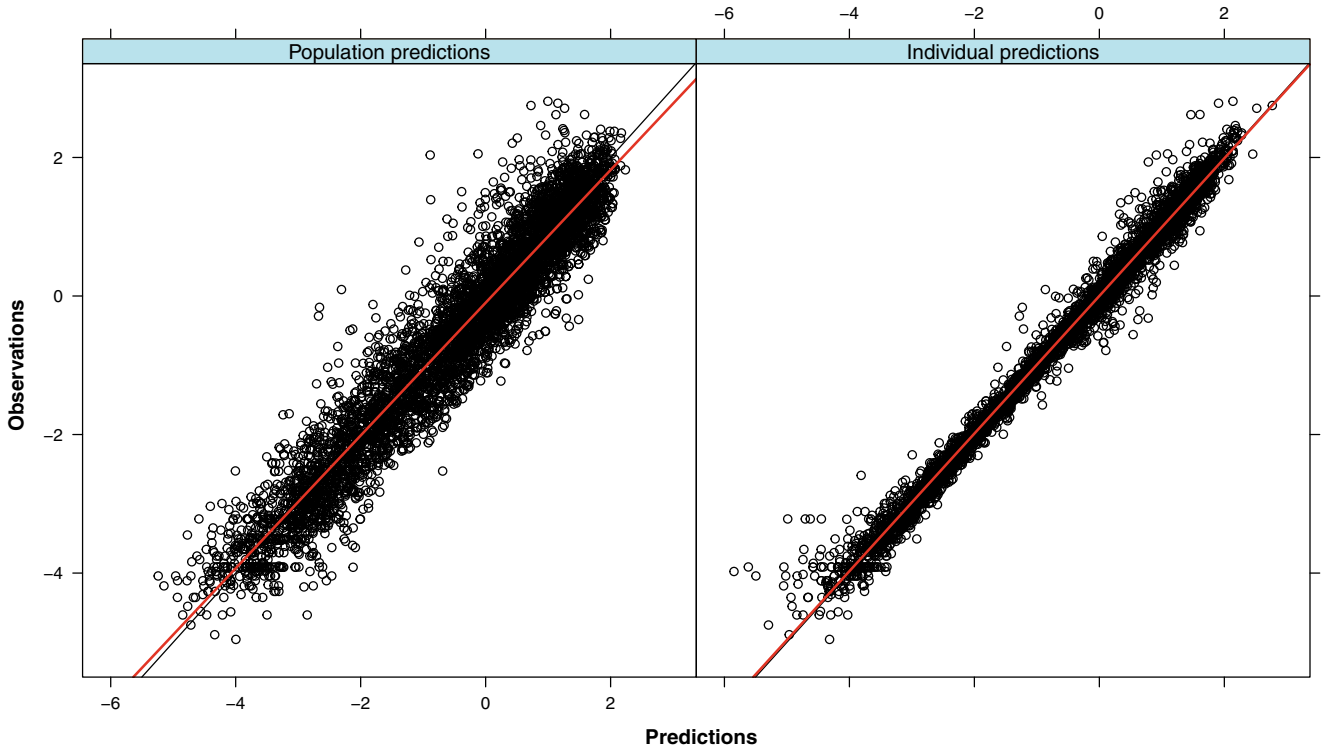

Fig. 2 Goodness-of-fit plots of the full covariate model including age with observed log-transformed paclitaxel concentrations versus, left panel: model predictions of log-transformed paclitaxel concentrations, and right panel: individual Bayesian predictions of log-transformed paclitaxel concentrations.

estimation of missing covariates were not within the scope of this study. For missing values, multiple imputation or mixture models were not performed. However, by introducing a separate estimate for the covariate bilirubin that contained missing data, it was precluded that missing data introduced bias. Furthermore, we evaluated whether the impact of age on

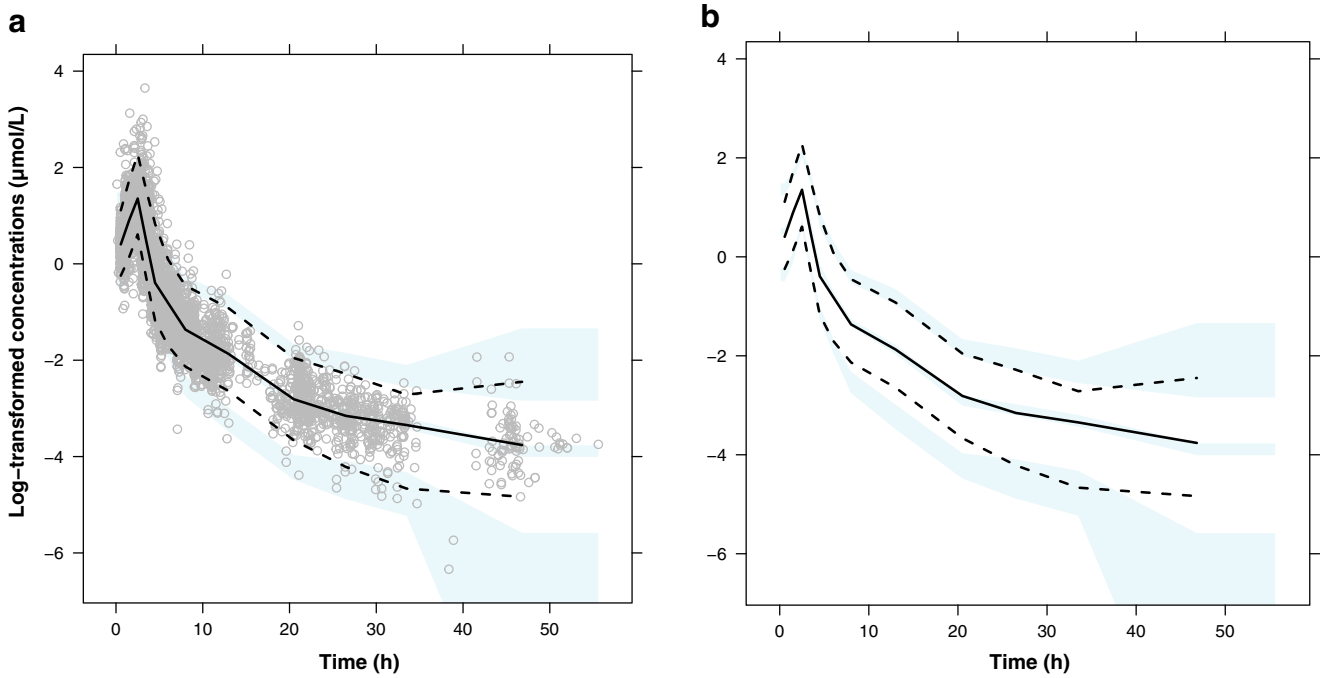

Fig. 3 Visual Predictive Check with $n = 1000$ of the full covariate model including age, (**a**) with observed concentrations, and (**b**) without observed concentrations plotted. Data concern log-transformed paclitaxel plasma concentrations, with the solid black line representing observed median concentrations, and dashed grey lines representing the observed 5th and 95th percentiles. Light grey areas indicate the 95% CIs of the 5^{th} and 95^{th} percentile of the predictions, and dark grey areas indicate the CI of the median. The dots in panel **a** are the observed concentrations.

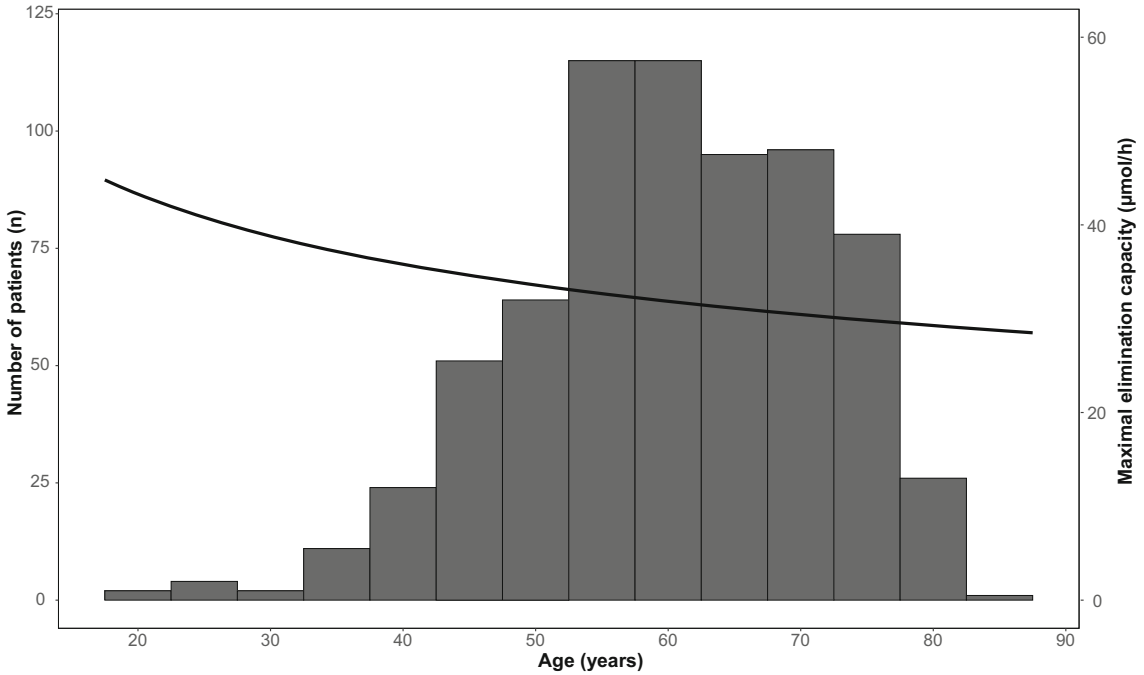

Fig. 4 Age as a continuous variable plotted against maximal elimination capacity of paclitaxel, with the line representing maximal elimination capacity (VM_{EL}) of paclitaxel and grey bars reflecting the patient distribution per 5-year age group in the total cohort.

paclitaxel PK may be distorted by performance status, by separately evaluating this covariate. Performance status did not alter our conclusion regarding the impact of age on paclitaxel PK.

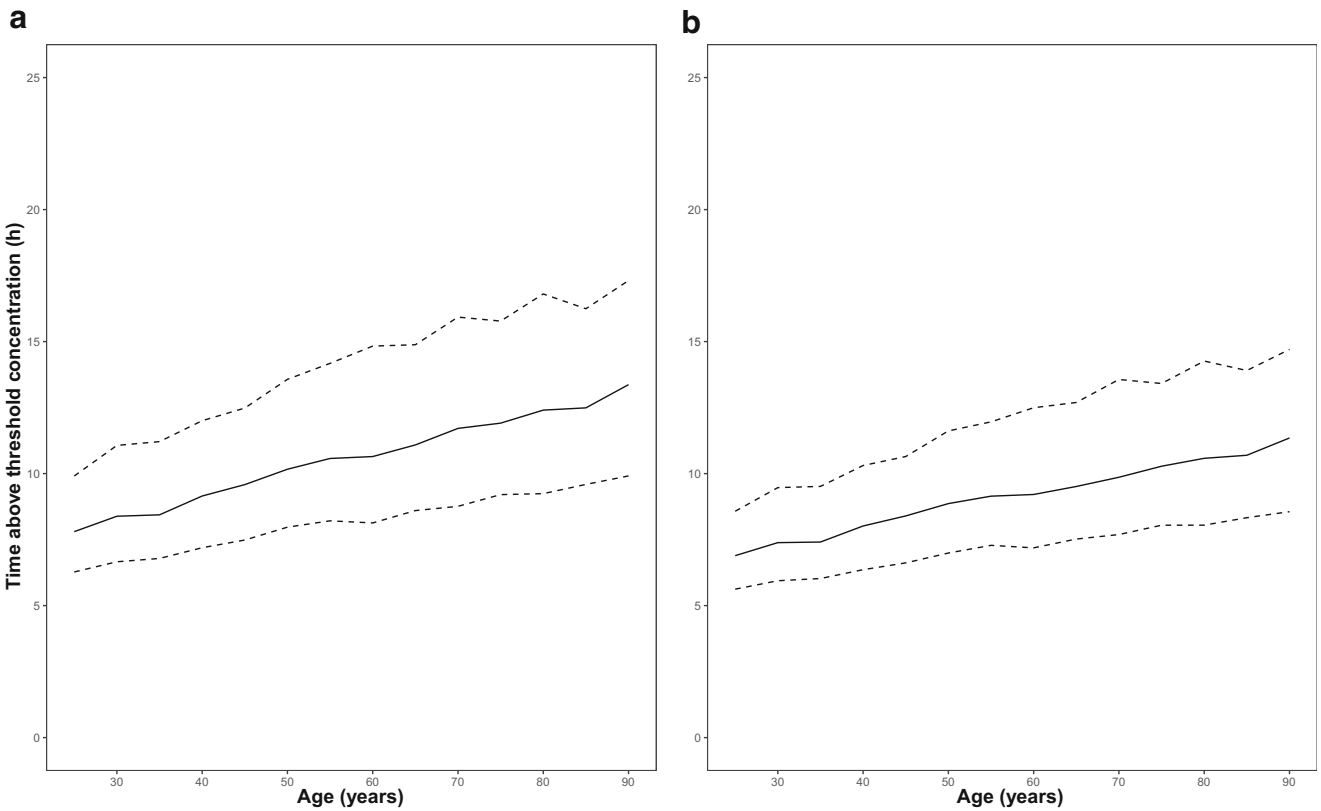

Fig. 5 Data simulation of the effect of age in (**a**) female patients and (**b**) male patients on the time-above-threshold concentration of 0.05 μmol/L, with paclitaxel administered at 80 mg/m^2 in a 1-h infusion.

In this extensive dataset including a considerable number of older patients, older age had only minor impact on paclitaxel PK. This study showed that there is no PK basis for a potentially increased risk of developing paclitaxel-related neutropenia in elderly patients.

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Jos H. Beijnen and Jan H.M. Schellens are (part-time) employees and shareholders of Modra Pharmaceuticals, and (partly) hold a patent on oral taxane pharmaceutical formulations. The other authors declare no conflicts of interest in connection with this manuscript. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees and was carried out in accordance with International Conference on Harmonsation Guidelines for Good Clinical Practice. Written informed consent was obtained from all individual participants.

REFERENCES

1. NNoone A, Cronin KA, Altekruse SF, Howlader N, Lewis DR, Petkov VI, *et al.* Cancer incidence and survival trends by subtype using data from the Surveillance Epidemiology and End Results Program, 1992–2013. Cancer Epidemiol Biomarkers Prev. 2017;26:632–41. https://doi.org/10.1158/1055-9965.EPI-16-0520.
2. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, *et al.* Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003;21:1383–9. https://doi.org/10.1200/JCO.2003.08.010.
3. Aapro MS, Köhne C-H, Cohen HJ, Extermann M. Never too old? Age should not be a barrier to enrollment in Cancer Clinical trials. Oncologist. 2005;10:189–204. https://doi.org/10.1634/theoncologist.2008-0207.
4. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: A 7-year experience by the US Food and Drug Administration. J Clin Oncol. 2004;22:4626–31. https://doi.org/10.1200/JCO.2004.02.175.
5. Freedman RA, Dockter TJ, Lafky JM, Hurria A, Muss HJ, Cohen HJ, *et al.* Promoting accrual of older patients with Cancer to Clinical trials : an Alliance for Clinical trials in oncology member survey (A171602). Oncologist. 2018;23:1–8. https://doi.org/10.1634/theoncologist.2018-0033.
6. Lucas C, Byles J, Martin JH. Medicines optimisation in older people: taking age and sex into account. Maturitas. 2016;93:114–20. https://doi.org/10.1016/j.maturitas.2016.06.021.
7. Dawson A, Dennison E. Measuring the musculoskeletal aging phenotype. Maturitas. 2016;93:13–7. https://doi.org/10.1016/j.maturitas.2016.04.014.
8. Seripa D, Panza F, Daragjati J, Paroni G, Pilotto A. Measuring pharmacogenetics in special groups: geriatrics. Expert Opin Drug Metab Toxicol. 2015;11:1073–88. https://doi.org/10.1517/17425255.2015.1041919.
9. Nakamura Y, Sekine I, Furuse K, Saijo N. Retrospective comparison of toxicity and efficacy in phase II trials of 3-h infusions of paclitaxel for patients 70 years of age or older and patients under 70 years of age. Cancer Chemother Pharmacol. 2000;46:114–8.
10. Lichtman SM, Hollis D, A a M, Rosner GL, C a R, Lester EP, *et al.* Prospective evaluation of the relationship of patient age and paclitaxel clinical pharmacology: Cancer and leukemia group B (CALGB 9762). J Clin Oncol. 2006;24:1846–51. https://doi.org/10.1200/JCO.2005.03.9289.
11. Food and Drug Administration. TAXOL (paclitaxel). In: NDA 020262; 2011.
12. Joerger M, Huitema ADR, van den Bongard DHJG, Schellens JHM, Beijnen JH. Quantitative effect of gender, age, liver function, and body size on the population pharmacokinetics of paclitaxel in patients with solid tumors. Clin Cancer Res. 2006;12:2150–7. https://doi.org/10.1158/1078-0432.CCR-05-2069.
13. Joerger M, Kraff S, Huitema ADR, Feiss G, Moritz B, Schellens JHM, *et al.* Evaluation of a pharmacology-driven dosing algorithm of 3-weekly paclitaxel using therapeutic drug monitoring: A pharmacokinetic-pharmacodynamic simulation study. Clin Pharmacokinet. 2012;51:607–17. https://doi.org/10.2165/11634210-000000000-00000.
14. De Graan AJM, Elens L, Smid M, Martens JW, Sparreboom A, Nieuweboer AJM, *et al.* A pharmacogenetic predictive model for paclitaxel clearance based on the DMET platform. Clin Cancer Res. 2013;19:5210–7. https://doi.org/10.1158/1078-0432.CCR-13-0487.
15. Kraff S, Nieuweboer AJM, Mathijssen RHJ, Baty F, De Graan AJ, Van Schaik RHN, *et al.* Pharmacokinetically based dosing of weekly paclitaxel to reduce drug-related neurotoxicity based on a single sample strategy. Cancer Chemother Pharmacol. 2015;75:975–83. https://doi.org/10.1007/s00280-015-2724-9.
16. De Graan AJM, Elens L, Sprowl JA, Sparreboom A, Friberg LE, Van Der Holt B, *et al.* CYP3A4*22 genotype and systemic exposure affect paclitaxel-induced neurotoxicity. Clin Cancer Res. 2013;19:3316–24. https://doi.org/10.1158/1078-0432.CCR-12-3786.
17. Hendrikx JJMA, Hillebrand MJX, Thijssen B, Rosing H, Schinkel AH, Schellens JHM, *et al.* A sensitive combined assay for the quantification of paclitaxel, docetaxel and ritonavir in human plasma using liquid chromatography coupled with tandem mass spectrometry. J Chromatogr B Anal Technol Biomed Life Sci. 2011;879:2984–90. https://doi.org/10.1016/j.jchromb.2011.08.034.
18. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (ICH) 2018.
19. Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn. 2001;28:481–504. https://doi.org/10.1023/A:1012299115260.
20. Ma C, Bandukwala S, Burman D, Bryson J, Seccareccia D, Banerjee S, *et al.* Interconversion of three measures of performance status: an empirical analysis. Eur J Cancer. 2010;46:3175–83. https://doi.org/10.1016/j.ejca.2010.06.126.
21. Stage TB, Bergmann TK, Kroetz DL. Clinical Pharmacokinetics of paclitaxel monotherapy: an updated literature review. Clin Pharmacokinet. 2018;57:7–19. https://doi.org/10.1007/s40262-017-0563-z.
22. Smorenburg CH, Ten Tije AJ, Verweij J, Bontenbal M, Mross K, Van Zomeren DM, *et al.* Altered clearance of unbound paclitaxel in elderly patients with metastatic breast cancer. Eur J Cancer. 2003;39:196–202. https://doi.org/10.1016/S0959-8049(02)00611-1.
23. Fidias P, Supko JG, Martins R, Boral A, Carey R, Grossbard M, *et al.* Measurement and impact of co-morbidity in elderly patients with advanced non-small cell lung cancer treated with

chemotherapy. A phase II study of weekly paclitaxel. Clin Cancer Res. 2001;7:3942–9. https://doi.org/10.1080/02841860600833178.
24. Sehl M, Sawhney R, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part II. Cancer J. 2005;11:461–73. https://doi.org/10.1097/00130404-200511000-00005.
25. Henningsson A, Karlsson MO, Viganò L, Gianni L, Verweij J, Sparreboom A. Mechanism-based pharmacokinetic model for paclitaxel. J Clin Oncol. 2001;19:4065–73.
26. Mielke S, Sparreboom A, Steinberg SM, Gelderblom H, Unger C, Behringer D, *et al.* Association of Paclitaxel Pharmacokinetics with the development of peripheral neuropathy in patients with advanced Cancer. Clin Cancer Res. 2005;11:4843–50. https://doi.org/10.1158/1078-0432.CCR-05-0298.
27. Mielke S, Sparreboom A, Behringer D, Mross K. Paclitaxel pharmacokinetics and response to chemotherapy in patients with advanced cancer treated with a weekly regimen. Anticancer Res. 2005;25:4423–7.
28. Gianni BL, Kearns CM, Giani A, Capri G, Vigan L, Locatelli A, *et al.* Nonlinear Pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/Pharmacodynamic relationships in humans. J Clin Oncol. 1995;13:180–90.
29. Ohtsu T, Sasaki Y, Tamura T, Nishiwaki Y, Clinical Pharmacokinetics SN. Pharmacodynamics of paclitaxel: A 3-hour infusion versus a 24-hour infusion. Clin Cancer Res. 1995;1:599–606.
30. Joerger M, von Pawel J, Kraff S, Fischer JR, Eberhardt W, Gauler TC, *et al.* Open-label, randomised study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small cell lung cancer (NSCLC). Ann Oncol. 2016;27:1895–902. https://doi.org/10.1093/annonc/mdw290.
31. Bhalla KN, Kumar GN, Walle UK, Ibrado AM, Javed T, Stuart RK, *et al.* Phase I and pharmacologic study of a 3-hour infusion of paclitaxel followed by cisplatinum and 5-fluorouracil in patients with advanced solid tumors. Clin Cancer Res. 1999;5:1723–30.
32. Kurata T, Tamura T, Shinkai T, Ohe Y, Kunitoh H, Kodama T, *et al.* Phase I and pharmacological study of paclitaxel given over 3 h with cisplatin for advanced non-small cell lung cancer. Jpn J Clin Oncol. 2001;31:93–9.
33. De Jongh FE, De Wit R, Verweij J, Sparreboom A, Van den Bent MJ, Stoter G, *et al.* Dose-dense cisplatin/paclitaxel: A well-tolerated and highly effective chemotherapeutic regimen in patients with advanced ovarian cancer. Eur J Cancer. 2002;38:2005–13. https://doi.org/10.1016/S0959-8049(02)00242-3.
34. Belani BCP, Kearns CM, Zuhowski EG, Erkmen K, Hiponia D, Zacharski D, *et al.* Phase I trial , including pharmacokinetic and Pharmacodynamic correlations, of combination paclitaxel and carboplatin in patients with metastatic non–small-cell lung Cancer. J Clin Oncol. 1999;17:676–84.
35. Huizing MT, van Warmerdam LJ, Rosing H, Schaefers MC, Lai A, Helmerhorst TJ, *et al.* Phase I and pharmacologic study of the combination paclitaxel and carboplatin as first-line chemotherapy in stage III and IV ovarian cancer. J Clin Oncol. 1997;15:1953–64. https://doi.org/10.1200/JCO.1997.15.5.1953.
36. Moreira A, Lobato R, Morais J, Silva S, Ribeiro J, Figueira A. Influence of the interval between the administration of doxorubicin and paclitaxel on the pharmacokinetics of these drugs in patients with locally advanced breast cancer. Cancer Chemother Pharmacol. 2001;48:333–7. https://doi.org/10.1007/s002800100297.