

# A pharmacometrics model to define docetaxel target in early breast cancer

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**Aims:** We aimed to study the relation between pharmacokinetics (PK) and pharmacodynamics (PD) of docetaxel in early breast cancer and recommend a target exposure.

**Methods:** A PK/PD study was performed in 27 early breast cancer patients treated with doxorubicin and cyclophosphamide for 4 cycles followed by 4 cycles of docetaxel 75–100 mg/m<sup>2</sup> infused every 21 days. Individual Bayesian estimates of docetaxel PK parameters were obtained using a nonparametric population PK model developed with data from patients with metastatic breast cancer who received dose-intensified docetaxel (300–350 mg/m<sup>2</sup>). Docetaxel area under the curve (AUC) and maximum concentration (C<sub>max</sub>) in each cycle and total cumulative AUC (AUC<sub>cum</sub>) were calculated and related to the incidence of adverse effects and tumour recurrence.

**Results:** Docetaxel clearance showed no change over the 4 treatment cycles, but a gradual increase in the volume of distribution was observed. One third of the patients had at least 1 dose reduction of docetaxel due to toxicity. The mean AUC, AUC<sub>cum</sub> and C<sub>max</sub> in patients showing docetaxel-associated adverse events were significantly higher than in patients free of toxicity ( $P < .05$ ). Fatigue and decrease in haemoglobin and haematocrit levels were related to docetaxel AUC and C<sub>max</sub> and pain to AUC. AUC and C<sub>max</sub> >4.5 mg\*h/L and 3.5 mg/L, respectively, were risk factors for docetaxel toxicity, while an AUC <4.5 mg\*h/L was associated with tumour recurrence.

**Conclusion:** We report for the first time a relation between docetaxel exposure and toxicity and recommend specific targets of drug exposure with implications for the clinical management of early breast cancer patients.

## KEYWORDS

breast cancer, docetaxel, pharmacodynamics, pharmacokinetics, precision medicine

## 1 | INTRODUCTION

The taxanes paclitaxel and docetaxel currently have a prominent role in the treatment of breast cancer based on solid evidence

resulting from a large amount of data from numerous trials including tens of thousands of patients. The pharmacodynamic (PD) differences between the 2 taxanes have been described demonstrating the concentration-dependent effect of docetaxel vs. the time-dependent effect of paclitaxel, which is essential for patient management.<sup>1–3</sup>

José Manuel Armendía was the principal investigator of this work.

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Several population pharmacokinetic (PK) models of docetaxel have been reported in patients of Asian ethnicity, the elderly, individuals with liver dysfunction, nonsmall-cell lung cancer and breast cancer, among others, but none in early breast cancer.<sup>4-8</sup> These PK models identified physiological and pathological variables responsible for the high interindividual variability in docetaxel PK that could be considered for a more precise, individualized dose adjustment instead of only using body surface<sup>9-11</sup> Serum  $\alpha$ -1-acid-glycoprotein level, which is increased during generalized infection, has been shown to significantly affect docetaxel clearance probably related to an inhibitory effect of the activity of cytochrome P450 3A4, which is mainly responsible for the metabolism of docetaxel.<sup>4,12</sup> Others have focused on the activity of ABCB1 and SCL01B3 membrane transporters affecting docetaxel metabolism and therefore drug exposure.<sup>13,14</sup>

Minimizing interindividual variability to attain an adequate docetaxel systemic exposure is of paramount importance due to its association with clinical response both in terms of efficacy<sup>15-17</sup> and toxicity<sup>18-20</sup> supporting the implementation of therapeutic drug monitoring in clinical practice.<sup>21-23</sup> Nevertheless, very few studies have reported quantitative targets for docetaxel exposure, and no information of the target therapeutic range is available for patients with early breast cancer.<sup>24</sup>

Therefore, the aim of this study was to guide docetaxel dose in early breast cancer patients using a population PK model developed in metastatic breast cancer patients and to study the relation between PK/PD both in terms of efficacy and toxicity for treatment optimization in the clinical practice.

## 2 | METHODS

### 2.1 | Patients and treatment protocols

The present study followed the tenets of the Declaration of Helsinki and institutional review board approval was obtained. Written informed consent was obtained from all patients.

To calculate the individual PK parameters of patients with early breast cancer and thereafter the PK/PD relationship, the analysis was conducted in 2 parts. First, a population PK model for docetaxel was developed based on data partially published and obtained from 27 patients with metastatic breast cancer resistant to standard chemotherapy and good functional status who received intensified treatment with docetaxel (300–350 mg/m<sup>2</sup> according to clinical decision) as previously described.<sup>25</sup>

Then, patients with localized breast cancer ( $n = 27$ ) were consecutively studied. Inclusion criteria are detailed in the supporting information, and patient characteristics of both the metastatic and nonmetastatic groups are listed in Table 1.

The AC-T scheme was administered every 21 days for 4 cycles, consisting of doxorubicin (A) and cyclophosphamide (C) at doses of 60 mg/m<sup>2</sup> administered over 30 minutes and 600 mg/m<sup>2</sup> over 90 minutes, respectively. Thereafter, 4 cycles of docetaxel (T) 21 days apart were administered at a dose of 75 or 100 mg/m<sup>2</sup>

### What is already known about this subject

- Docetaxel has a prominent role in the treatment of metastatic breast cancer.
- High interindividual variability in docetaxel pharmacokinetics has been extensively published related to physiological and pathological variables and may attempt against achieving an adequate docetaxel exposure in relation to efficacy and toxicity.
- Docetaxel dose optimization in early breast cancer patients is an unmet medical need, and population pharmacokinetics is a useful tool to attain this goal.

### What this study adds

- This study provides evidence that docetaxel systemic exposure is related to the taxane-associated adverse events.
- We observed a tendency in the relation between docetaxel systemic exposure and probability of tumour recurrence.
- According to our data, we recommend a target docetaxel systemic exposure of 4.5 mg\*h/L/cycle and a maximum plasma concentration of 3.5 mg/L to obtain optimal benefit from the balance between the incidence of adverse events and the probability of antitumor activity.

over 60 minutes depending on axillary lymph-node involvement. Prophylaxis of severe neutropenia with granulocyte colony-stimulating factor (G-CSF) was used in all patients receiving docetaxel at 100 mg/m<sup>2</sup> and in 4 others receiving a dose of 75 mg/m<sup>2</sup> during treatment maintenance (supporting information). Premedication for prophylaxis of allergic reactions and oedema consisted of dexamethasone (8 mg, twice daily) administered from days -1 to +3 or methylprednisolone (40 mg, twice daily) in 6 doses starting on day -1. Further details of patient inclusion criteria are detailed in the supporting information.

### 2.2 | Sampling strategy and bioanalysis

An extensive sampling strategy was used in patients from Group I. As the aim of the previous study was to characterize gemcitabine PK and as docetaxel was concomitantly administered, we used this rich sampling to characterize docetaxel PK. Thereby 9 samples were obtained for each patient prior to drug administration, 60 minutes after infusion initiation, and at 0.083, 0.25, 0.75, 1.5, 5, 12 and 24 hours after infusion.

**TABLE 1** Anthropometric and demographic variables of patients included in metastatic (Group I) and early breast cancer patients (Group II)

Variable	Mean	SD	Range
<b>Group I (metastatic breast cancer patients, n = 27)</b>			
Age (y)	44.15	6.16	33–56
Weight (kg)	64.70	8.65	51–87
Height (cm)	162	5.51	152–172
BSA (m <sup>2</sup> ) <sup>a</sup>	1.69	0.12	1.5–2.0
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	23.2		20–33
Obesity			
No	23		
Yes	4		
<b>Group II (early breast cancer patients, n = 27)</b>			
Age (y)	48.33	10.9	28–75
Weight (kg)			51.6–116
Height (cm)	161	6.18	152–172
BSA (m <sup>2</sup> ) <sup>a</sup>	1.66		1.6–2.1
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	24.5		18–51
Obesity			
No	25		
Yes	2		

BMI, body mass index; BSA, body surface; SD, standard deviation.

<sup>a</sup>Data are expressed as median (range).

To calculate the individual Bayesian estimates of the PK parameters of Group II patients, venous blood samples were limited as some of them required total lymphadenectomy, which complicated venous access. Therefore, we used a limited sampling strategy based on previous information about the most informative sampling times<sup>21</sup> along with clinically feasible sampling strategies as follows: (i) 0.5 hours after the start of the infusion, 0.167 and 2 hours postinfusion; (ii) 0.25, 0.33 and 3 hours postinfusion; (iii) 0.5 hours after the start of the infusion, and 0.5 and 4 hours postinfusion; and (iv) 0.25 hours before the end of the infusion and 1 and 5 hours postinfusion.

Then, plasma was separated and stored at  $-30^{\circ}\text{C}$  until analysis by high-performance liquid chromatography according to a previously reported method.<sup>26</sup>

### 2.3 | PK analysis and area under the curve guided dosing

The population PK parameters of docetaxel were estimated using the nonparametric adaptive grid platform implemented in the MM-USC\*PACK program.<sup>27</sup> Both 2- and 3-compartment models were fitted to the concentration-time data, and model selection criteria were based on the Akaike, Schwartz and Bayesian information criteria, minimization of  $-2^* \log$ -likelihood, and goodness of fit plots.

In the nonparametric adaptive grid each concentration is weighted by the determinant of the Fisher information matrix (inverse

of variance) and corrected by  $\gamma$  as an estimate of the overall contribution of the remaining environmental sources of intraindividual variability. For the first term, the standard deviation of each observation was calculated based on the bioanalytical assay error polynomial and the polynomial coefficients were estimated from the quantification in triplicates of 8 samples of known concentrations between 0.05 and 12 mg/L.<sup>28</sup>

The predictive performance of the model was evaluated according to the bias or mean prediction error (MPE) and the imprecision, calculated as the root mean squared error (RMSE).

Advanced internal validation was performed by means of bootstrap using SPLUS.<sup>29</sup> The model was considered reliable if the bootstrap estimates of the PK parameters were within the 95% confidence interval (CI) of the PK parameters calculated with the original dataset.

The PK parameters estimated from data of Group I were used as priors for the subsequent maximum a posteriori Bayesian estimation (MAP-BE) of the individual PK parameters of patients from Group II using the Bayesian adaptive control module of the USC\*PACK v11.2.<sup>30</sup> The estimated individual docetaxel PK included area under the curve (AUC) in the central (cAUC) and peripheral compartment in each cycle, cumulative AUC (cAUCcum) in central compartment, and maximum concentration (Cmax) in the central (cCmax) and peripheral compartments.

Afterwards, dose adjustment in early breast cancer patients was performed to reach the intended target of 3.7 or 4.9 mg\*L/h for docetaxel 75 or 100 mg/m<sup>2</sup>, respectively, as previously proposed.<sup>21</sup>

### 2.4 | Study covariates

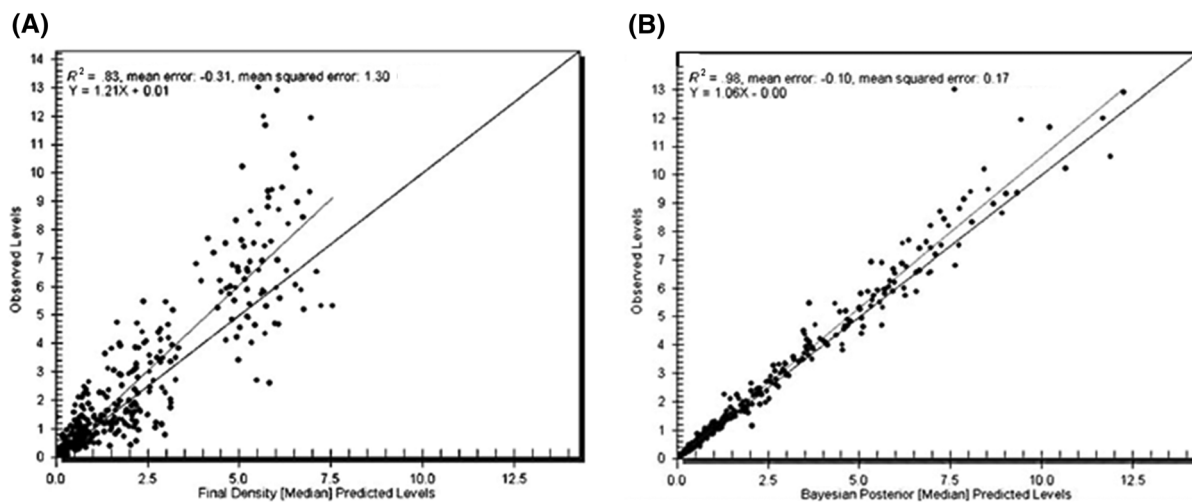
The following data were collected from the electronic records of the hospital: anthropometric variables (current weight, ideal body weight estimated by the Devine formula, height, body surface area, body mass index both as a continuous and a categorical variable); twice daily demographic variables (sex and age); treatment variables (dose and dosage of docetaxel, date of treatment and cycle number); pathophysiological variables (date of diagnosis, TNM staging of the tumour, comorbidities and Eastern Cooperative Oncology Group performance status score); and biochemical variables (kidney and liver function tests, albumin,  $\alpha$ -1-acid glycoprotein, serial blood counts, tumour markers and clinical variables).

Toxicity was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.

Adjuvant! Online was used as a reference to calculate the expected survival in the study population.<sup>31</sup>

### 2.5 | Statistical analysis

Continuous variables were compared using the Student *t* or the Mann–Whitney *U* test, while categorical variables were evaluated by means of the Fisher's exact test. The difference between the



**FIGURE 1** Goodness of fits plots. (A) Residual plot compared to individual predicted median concentrations using the final model. (B) Individual predicted vs. observed docetaxel concentrations

population median and 95% CI between groups was estimated according to the Hodges–Lehmann method. For overall survival analysis, the Kaplan–Meier method was used considering survival time from the date of histological tumour diagnosis and death of the patient as an event regardless of the cause. None of the patients in the study were lost to follow-up. For progression-free survival, local or distant tumour recurrence was considered as an event.

Statistical analysis was performed using SPSS v 15.0 software, and the association between docetaxel-related adverse effects and systemic exposure (AUC and Cmax) was assessed by logistic regression using R software.

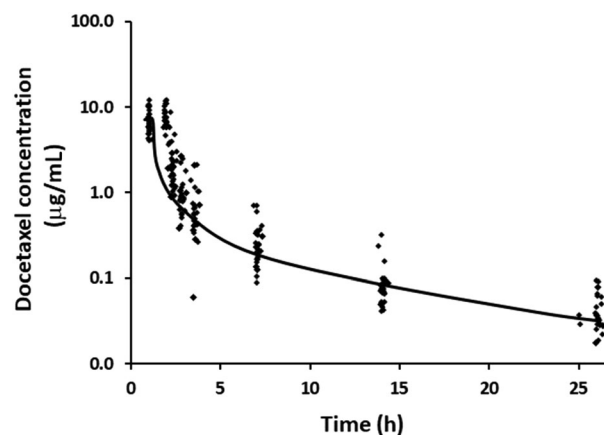
### 3 | RESULTS

#### 3.1 | Population model of docetaxel in patients with advanced breast cancer (*a priori* information)

A total of 235 samples corresponding to 8.7 samples per patient were available for the analysis. A 2-compartment model with linear elimination best described docetaxel PK, although a nonlinear distribution was observed in 3 patients as previously described.<sup>32</sup> Diagnostic plots (Figures 1 and 2) showed that the model had an overall good fit. Likewise, the MSE and the RMSE were  $-0.091$  and  $0.113$ , respectively, and the interquartile range included zero suggesting a lack of systematic errors.

The final values for the polynomial coefficients to describe the error equation of the analytical method for docetaxel were standard deviation =  $0.01148 + 0.06638C$  ( $R^2$ : 0.975), and the gamma coefficient was 1.683.

Mean values of the PK parameter estimated using the final model were similar to those obtained from the bootstrap replications and within the 95% CI indicating the robustness of the model (Table 2).



**FIGURE 2** Concentration–time profile of docetaxel in advanced breast cancer patients (group 1) and model prediction. The line shows the best prediction for a typical patient.

#### 3.2 | Bayesian parameter estimation in early breast cancer

Demographic and anthropometric characteristics of early breast cancer patients are listed in Table 1, while treatment variables and tumour characteristics are presented in the supporting information showing that biochemical parameters were similar to those of Group I patients.

Overall, 76.5% of the cycles were administered during the morning hours over a 66-min infusion (coefficient of variance, 16%).

Twenty-six patients received all 4 scheduled cycles of docetaxel; only 1 patient received 3 cycles because she developed Guillain–Barré syndrome. In addition, technical mistakes in sampling and infusion rates resulted in 77 chemotherapy cycles that were finally included in the analysis corresponding to 71% of the cycles administered.

**TABLE 2** Docetaxel population pharmacokinetic parameters and internal validation in metastatic breast cancer (Group I)

Parameter	Model		Bootstrap		
	Mean (SD)	95% CI	Mean (SD)	Interquartile range	Bias
K ( $\text{h}^{-1}$ )	4.955 (0.499)	2.122–7.690	4.923 (0.296)	4.426–5.405	0.0015
$K_{12}$ ( $\text{h}^{-1}$ )	1.808 (0.669)	0.728–3.987	1.781 (0.144)	1.569–2.048	–0.004
$K_{21}$ ( $\text{h}^{-1}$ )	0.323 (0.101)	0.205–0.657	0.314 (0.020)	0.287–0.356	0.0001
$V_s$ (L/kg)	0.110 (0.137)	0.047–0.180	0.110 (0.008)	0.100–0.126	–0.0001

k, elimination rate constant;  $k_{12}$ , distribution rate constant from the central to the peripheral compartment;  $k_{21}$ , distribution rate constant from the peripheral to the central compartment; SD, standard deviation;  $V_s$ , volume of distribution from the central compartment; 95% CI, 95% mean confidence interval.

**TABLE 3** (a) Statistics of the individual docetaxel pharmacokinetic parameters of early breast cancer patients and (b) pharmacokinetic parameters according to cycle of docetaxel administration

(a)	Pharmacokinetic parameter				
	K ( $\text{h}^{-1}$ )	$K_{12}$ ( $\text{h}^{-1}$ )	$K_{21}$ ( $\text{h}^{-1}$ )	$V_s$ (L/kg)	CL (L/h/kg)
Mean	5.233	1.426	0.31	0.097	0.504
Median	5.29	1.491	0.294	0.096	0.515
SD	0.583	0.472	0.088	0.014	0.083
Min	3.479	0.203	0.217	0.046	0.279
Max	6.279	2.054	0.985	0.144	0.662
(b)	Cycle 1	Cycle 2	Cycle 3	Cycle 4	
$V_s$ (L/kg)	0.095 (0.091–0.099)	0.097 (0.093–0.102)	0.098 (0.093–0.104)	0.100 (0.094–0.106)	
CL (L/h/kg)	0.49 (0.45–0.52)	0.51 (0.48–0.54)	0.50 (0.46–0.54)	0.51 (0.47–0.56)	

Data are shown as median (95% confidence interval).

CL, clearance; k, elimination rate constant;  $k_{12}$ , distribution rate constant from the central to the peripheral compartment;  $k_{21}$ , distribution rate constant from the peripheral to the central compartment; SD, standard deviation;  $V_s$ , apparent volume of distribution from the central compartment.

First, we performed an external model validation using the dataset obtained from all early breast cancer patients. The dataset consisted of 272 samples obtained at different times after docetaxel administration. The estimation of bias and precision was 0.6% and 0.004%, respectively. Moreover, the median (range) observed docetaxel concentration was 0.520 mg/L (0.015–4.71), and the median (range) individual predicted concentration was 0.518 mg/L (0.02–4.65). Altogether, we consider that the performance of the model was acceptable to be used for docetaxel forecasting in clinical practice.

Statistics of individual docetaxel PK parameters are shown in Table 3. No significant differences were observed in docetaxel clearance among the 4 treatment cycles, with a mean value per cycle of 0.49, 0.51, 0.50 and 0.51 L/h/kg in cycles 1–4, respectively; however, the volume of distribution from the central compartment ( $V_s$ ) showed a gradual increase as the cycles progressed (0.095, 0.097, 0.098 and 0.100 L/kg in cycles 1–4, respectively) becoming statistically significant in the fourth cycle ( $P = .008$ ).

The estimated mean cAUC (95% CI) was 3.9 mg $\cdot$ h/L (3.7–4.1) for patients given the dosing scheme of 75 mg/m $^2$  and 4.7 mg $\cdot$ h/L (4.5–4.9) for those who received 100 mg/m $^2$ . As shown in Table 4, a gradual decrease in the cAUC was observed reaching statistically

significant differences in the third (–7.8%;  $P = .014$ ) and fourth (–11.7%;  $P = .001$ ) compared to the first cycle.

### 3.3 | PK/PD relationships in terms of toxicity and efficacy in early breast cancer

The toxicity observed in this group of patients was manageable, and a summary is detailed in Table 5. No infusion-related reactions were observed, and the incidence of vomiting was low probably due to patient management with antiemetics. All patients suffered alopecia grade 2 after AC therapy but 25 of 27 patients started hair recovery during docetaxel treatment.

One third of the patients had at least 1 dose reduction during docetaxel administration. Specifically, 3 of 13 patients who received docetaxel at 75 mg/m $^2$  and 6 of 14 who received 100 mg/m $^2$  required a dose reduction due to clinical observations of toxicity without significant differences in the incidence of dose reductions between dose groups ( $P = .122$ ).

Overall, the mean (95%CI) cAUC in cycles of patients that had grades 2–3 toxicity and required a dose reduction was 4.93 mg $\cdot$ h/L (4.20–5.67 mg $\cdot$ h/L), showing a trend towards higher exposure than

Parameter	Cycle 1 (n = 19)	Cycle 2	Cycle 3	Cycle 4
pAUC (mg*h/L)	4.63 (0.87)	4.4 (0.97)	4.33 (1.08)	4.09 (1.09)
pAUC (mg*h/L)	2.24 (0.97)	2.02 (1.07)	2.05 (1.09)	2.04 (1.05)
cCmax (mg/L)	3.32 (0.79)	3.47 (0.86)	3.26 (0.77)	3.09 (0.89)
Time to cCmax (h)	1.17 (0.25)	1.05 (0.07)	1.08 (0.13)	1.08 (0.15)
pCmax (µg/kg)	0.41 (0.16)	0.37 (0.17)	0.37 (0.16)	0.37 (0.15)
Tmax (h)	1.4 (0.2)	1.30 (0.12)	1.33 (0.10)	1.32 (0.13)
Distribution half-life (h <sup>-1</sup> )	0.10 (0.01)	0.1 (0.01)	0.10 (0.01)	0.1 (0.01)
Terminal half-life (h <sup>-1</sup> )	3.05 (0.42)	3.00 (0.45)	3.07 (0.57)	3.07 (0.64)

Data are shown as mean (standard deviation).

cCmax and cAUC, maximum concentration and area under the concentration–time profile, respectively; pCmax and pAUC, maximum concentration and area under the concentration–time profile in the peripheral compartment, respectively; Tmax, time to maximum concentration.

**TABLE 4** Individual pharmacokinetic parameters of docetaxel exposure by cycle in early breast cancer patients (Group II)

Toxicity	Grade 0	Grade I	Grade II	Grade III	Grade IV
Haematological toxicity					
Thrombocytopenia		1			
Hepatotoxicity					
TB	107	0	0	0	0
ALT	88	18	1	0	0
ASP	59	41	7	0	0
ALP	107	0	0	0	0
GGT	81	25	1	0	0
Gastrointestinal					
Mucositis	89	9	8	1	0
Diarrhoea	96	4	6	1	0
Constipation	103	0	4	0	0
Vomiting		1	1		
Neurotoxicity (pain)					
Myalgia	0	12	10	1	0
Arthralgia	0	1	2	0	0
Mixed	0	3	3	1	0
General disorders					
Fatigue	41	25	34	7	0
Others					
Watering eyes	0	5	0	0	0
Erythrodysesthesia	5	5	0	0	0
Nail changes	63	33	9	2	0

**TABLE 5** Toxicity of docetaxel in early breast cancer patients (number of cycles)

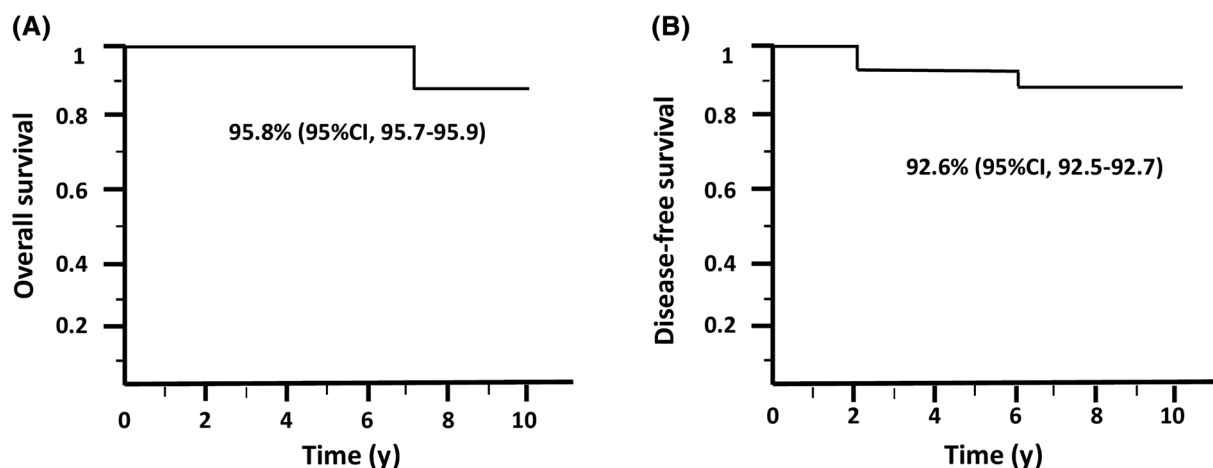
Three patients had febrile neutropenia after the first cycle, of whom 2 received 100 and 1 received 75 mg/m<sup>2</sup>, without granulocyte colony-stimulating factor support.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; TB, total bilirubin.

that attained in cycles without docetaxel-associated toxicity (cAUC of 4.29 mg\*h/L, 95%CI: 4.07–4.52;  $P = .071$ ). Also, the mean (95%CI) cCmax of the cycles with docetaxel-associated toxicity was significantly higher than the remaining cycles that were free of toxicity (3.49 mg/L, range: 2.83–4.15 vs. 3.26, range: 3.07–3.45;  $P = .0239$ ). Moreover, when exclusively evaluating the 9 patients (27 cycles) that

developed toxicity in at least 1 cycle and required dose reduction, the mean difference between docetaxel cAUC and cCmax in cycles with and without toxicity was 0.715 mg\*h/L (95%CI: 0.34–1.68,  $P = .003$ ) and 0.51 mg/L (0.10–0.91,  $P = .02$ ), respectively.

A detailed analysis by cycle of chemotherapy showed that 3 of the 5 patients who required a dose reduction after the first cycle



**FIGURE 3** (A) Overall survival and (B) progression-free survival. CI, confidence interval

had a higher cCmax (3.91, 4.12 and 4.91 mg/L) than the overall median of 3.2 mg/L (interquartile range: 2.61–4.01) attained in that cycle. The other 2 patients who showed toxicity in cycle 1 had a lower cCmax (2.06 and 2.17 mg/L) compared to the median value; however, they received 75 mg/m<sup>2</sup> of docetaxel without prophylactic G-CSF, which may explain the development of acute haematological toxicity. One patient with leukopenia in the second cycle had a cCmax of 2.5 mg/L after 75 mg/m<sup>2</sup> of docetaxel without prophylactic G-CSF. Another patient with grade 3 mucositis in the third cycle had a cCmax of 3.42 mg/L after receiving 100 mg/m<sup>2</sup> of docetaxel.

Considering that toxicity may be cumulative, we analysed docetaxel cumulative exposure. Significant associations were found between overall grade 2/3 toxicity and AUC<sub>cum</sub> of the central compartment (cAUC<sub>cum</sub>; OR, 2.01; 95% CI, 1.07–3.78; *P* = .002), peripheral AUC<sub>cum</sub> (OR, 1.99; 95%CI, 1.06–3.73; *P* = .003), cCmax, cum (OR, 1.55; 95% CI, 0.97–2.46; *P* = .029), and peripheral C<sub>max</sub>, cum (OR, 70.59; 95% CI, 1.30–3826; *P* = .004). Specifically, 1 patient who developed docetaxel-associated adverse events in the second cycle showed a cAUC<sub>cum</sub> of 9.9 mg\*h/L (4.95 mg\*h/L per cycle) compared to the mean cAUC<sub>cum</sub> of 9 mg\*h/L (95%CI: 8.5–9.5 mg\*h/ml) after 2 cycles in patients without toxicity. cAUC<sub>cum</sub> of the 2 patients who developed toxicity in the third cycle was 14.16 and 15.83 mg\*h/L (4.7 and 5.2 mg\*h/L per cycle, respectively), values considerably higher than the overall cumulative exposure of 13.25 mg\*h/L (4.4 mg\*h/L per cycle) and outside the 95% CI (95% CI: 12.5–13.95) of patients without signs of toxicity.

A thorough description of the correlations between toxicity and docetaxel PK is provided in the supporting information. Briefly, we observed significant associations between haematological (a decrease in haematocrit and haemoglobin levels), liver and neurological toxicity as well as with fatigue.

### 3.4 | Overall survival

Using Adjuvant! Online, the likelihood of remaining disease free 10 years after receiving the AC-T treatment scheme was 78%

(interquartile range, 67.5–81.5). However, after a median follow-up of 7.2 years, but in no case <6 years, the median overall survival was not reached. At the time of this analysis, 95.8% of the patients were alive, and 92.6% were disease free. Overall survival and disease-free survival curves are shown in Figure 3A,B, respectively.

The mean cAUC<sub>cum</sub> in patients who did not show disease recurrence was 17.25 mg\*h/L (95% CI, 15.8–18.7 mg\*h/L), while the cumulative exposure of the only 2 patients who relapsed were 11.8 and 15 mg\*h/L. Despite no significant difference could be encountered in the cAUC<sub>cum</sub> between patients with recurrence and those free of relapse (*P* > .05), we assume that both patients were not resistant to treatment but underexposed as re-exposure to higher doses allowed to rescue them from the tumour recurrence.

## 4 | DISCUSSION

The present study provides novel and unique information about the efficacy, safety and PK/PD relation of docetaxel in early breast cancer patients. As docetaxel was initially indicated for breast cancer metastasis with a high tumour burden, most PK studies were focused on this group, and only years later, its use was extended to patients with less severe breast tumours as is the case of our population. Thus, we developed a population PK model that was successfully used for docetaxel precision dosing describing the PK/PD relationships of docetaxel in patients with early breast cancer that may be useful for future patient management. In addition, we propose a therapeutic range based on our observations regarding docetaxel PK, toxicity and efficacy.

Although different population PK models of docetaxel were developed for metastatic breast cancer patients, here, we report for the first time a nonparametric population model that was successfully used as a clinical routine tool for dosing management based on drug exposure and the intended target in early breast cancer. Patients with advanced and metastatic tumours develop physio-pathological changes previously reported and that may affect docetaxel PK–PD relationship.<sup>12,32,33</sup> Despite scarce data being reported, previous

authors proposed systemic exposure targets for docetaxel; these values were based on clinical observations from patients with different types of tumours distinct from early breast cancer and without the development of a PK-PD study as we developed in the present report.<sup>34-37</sup>

A linear 2-compartment model adequately fitted the concentration-time data obtained in a previous cohort of metastatic patients at our centre. Compared to previous publications, Slaviero *et al.*<sup>38</sup> reported a mean value for  $k$ ,  $V_s$  and CL of  $3.8 \text{ h}^{-1}$ , 7.9 L and 30.1 L/h, close to our results of  $4.5 \text{ h}^{-1}$ , 7.7 L and 35.2 L/h, respectively. Moreover, McLeod *et al.*<sup>39</sup> reported a  $V_s$  similar to that obtained in our population. Nonetheless, none of the previous models were developed only in breast cancer patients but different solid tumours.

In our cohort of patients with early breast cancer, docetaxel CL remained unaltered throughout the 4 treatment cycles. Despite the absence of temporal changes in the parameter related to docetaxel elimination, a decrease in mean cAUC was observed while the number of cycles progressed, which may be explained by intentional dose reduction due to clinical toxicity. By contrast,  $V_s$  progressively increased and reached statistical significance in the fourth docetaxel cycle (5%). This finding is not unexpected, as it is well known that fluid retention is a frequent docetaxel-related toxicity, which in extreme cases may lead to systemic capillary leak syndrome and even pulmonary oedema.<sup>40</sup> This toxicity is more likely after the administration of at least 4 cycles of docetaxel and may be reduced by the prophylactic use of corticosteroids.

In our study, overall toxicity was manageable. However, 1/3 of our patients needed dose reductions due to toxicity, accounting for 23 and 43% of those who received docetaxel 75 and 100 mg/m<sup>2</sup>, respectively, supporting the concept of dose-dependent toxicity of the taxane.

Our study is the first to show a correlation between systemic exposure and docetaxel-associated adverse events in early breast cancer patients. Patients with a mean cAUC of 4.9 mg\*h/L and range between 4.2 and 5.7 mg\*h/L manifested adverse events that were absent in patients with a mean value of 4.3 mg\*h/L and range between 4.1 and 4.5 mg\*h/L. Therefore, our data indicate that patients with a cAUC >4.5 mg\*h/L are more likely to develop toxicity, and, therefore, we recommend this value as a cutoff for routine clinical management. In addition, a C<sub>max</sub> of 3.5 mg/L is recommended as a target for docetaxel dosing management.

Cumulative exposure to docetaxel in both the central and peripheral compartments, measured as AUC or C<sub>max</sub>, displayed a significant relation to docetaxel-associated adverse events again with a value of 4.5 mg\*h/L as a threshold for increased incidence of toxicity. This observation supports the use of a PK-guided approach instead of the conventional dosing by body surface area.

In correspondence with previous studies, our data suggest that acute toxicity is related to C<sub>max</sub> and chronic toxicity to AUC as we observed a relation between myelotoxicity and C<sub>max</sub>, while fatigue was closely related to AUC and developed after 3 or 4 cycles of docetaxel.<sup>41-43</sup>

The association between docetaxel PK and haematological toxicity has been previously evaluated. Several authors found a significant relationship between docetaxel PK and haematological toxicity,<sup>19,44,45</sup> while others<sup>46</sup> did not find such a relationship. In our study, no significant changes were observed in leucocyte, neutrophil or lymphocyte counts throughout docetaxel treatment probably due to prophylactic G-CSF. Regarding red-blood-cell counts, a significant decrease in haematocrit and haemoglobin was observed after the first cycle stabilizing afterwards. Similarly, other authors described a significant relationship between docetaxel AUC and anaemia.<sup>47</sup>

In our patients, liver toxicity was only mild (grades 1-2). Of the liver enzymes, alanine aminotransferase was most frequently elevated with an incidence of grade 1 in 38% and grade 2 in 6.5% of the cycles. A positive correlation between docetaxel exposure and alanine aminotransferase levels was found with a trend towards statistical significance. Our results are in line with those of Goh *et al.*<sup>10</sup> who found that decreased docetaxel clearance, as seen in patients with high glutamate pyruvate transaminase levels, was related to increased toxicity explained by the consequent greater systemic exposure.

Prophylactic administration of G-CSF for the prevention of docetaxel-related haematological toxicity is associated with a 20% incidence of bone pain.<sup>48</sup> In our study, bone, joint and nail pain was observed in 35% of the cycles, and neurotoxicity was significantly related to docetaxel exposure, although reversible in all cases.

Fatigue occurs in approximately 30% of breast cancer patients and in disease-free survivors.<sup>49</sup> In our cohort, the incidence of grade 2/3 fatigue was higher in the third and fourth than in the earlier cycles, with a significant correlation between central and peripheral AUC showing that this type of toxicity results from cumulative taxane exposure.

Overall and progression-free survival was excellent. After a median follow-up of 7.2 years, more than 95% of patients were disease free, which is higher than most studies reporting a 5-year disease-free survival ranging between 70 and 91%. Noteworthy, both patients that recurred received 75 mg/m<sup>2</sup> docetaxel and reached a cC<sub>max</sub> of 2.0 and 2.7 mg/L and a cumulative cAUC of 15 and 11.8 mg\*h/L after 4 cycles of chemotherapy. Despite the limited number of events, our data suggest that treatment effectiveness is related to cumulative exposure in the central compartment and that the optimal PK target for cAUC is between 4.3 and 4.5 mg\*h/L.

In our PK/PD study in early breast cancer patients, we aimed to develop a tool to establish a dose that is both effective and safe for routine clinical management. Our results suggest that toxicity may be an adequate target for monitoring docetaxel in the AC-T scheme. When the drug is administered in monotherapy with prophylactic administration of G-CSF, we suggest a cC<sub>max</sub> ≤3.5 mg/L to minimize the incidence of adverse events. In addition, to reduce cumulative toxicity and to increase the probability of efficacy, we propose a target exposure of 4.5 mg\*h/L per cycle resulting in a maximum cumulative systemic exposure of 18 mg\*h/mL after 4 cycles of docetaxel.

In conclusion, in the present study, we developed a clinically relevant population PK model of docetaxel for early breast cancer



patients. The study of the relationship between docetaxel exposure and toxicity resulted in a proposed target to optimize treatment with docetaxel in this population. We propose a target for docetaxel exposure to achieve a balance between safety and efficacy.

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## COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## CONTRIBUTORS

A.A. and J.M.A. conceived the study; JMA was the oncologist responsible for patient treatment; A.A. performed the PK analysis; A.A. and J.M.A. performed the statistical analysis. A.A. and P.S. verified the analytical methods; A.A., J.M.A. and P.S. performed data analysis. All authors discussed the results, contributed to the writing of the manuscript and agreed on the final version of the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

- Sanli UA, Uslu R, Karabulut B, et al. Which dosing scheme is suitable for the taxanes? An in vitro model. *Arch Pharm Res.* 2002;25(4):550-555. doi:10.1007/BF02976617
- Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol.* 2003;21(8):1431-1439. doi:10.1200/JCO.2003.09.081
- Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med.* 2008;358(16):1663-1671. doi:10.1056/NEJMoa0707056
- Bruno R, Hille D, Riva A, et al. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. *J Clin Oncol.* 1998;16(1):187-196. doi:10.1200/JCO.1998.16.1.187
- Hooker AC, Ten Tije AJ, Carducci MA, et al. Population pharmacokinetic model for docetaxel in patients with varying degrees of liver function: incorporating cytochrome P4503A activity measurements. *Clin Pharmacol Ther.* 2008;84(1):111-118. doi:10.1038/sj.cpt.6100476
- Minami H, Kawada K, Sasaki Y, et al. Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice. *Cancer Sci.* 2009;100(1):144-149. doi:10.1111/j.1349-7006.2009.00992
- Crombag MBS, Dorlo TPC, van der Pan E, et al. Exposure to docetaxel in the elderly patient population: a population pharmacokinetic study. *Pharm Res.* 2019;15(12):181. doi:10.1007/s11095-019-2706-4
- Kenmotsu H, Tanigawara Y. Pharmacokinetics, dynamics and toxicity of docetaxel: why the Japanese dose differs from the Western dose. *Cancer Sci.* 2015;106(5):497-504. doi:10.1111/cas.12647
- Nieuweboer AJ, de Morree ES, de Graan AJ, et al. Inter-patient variability in docetaxel pharmacokinetics: a review. *Cancer Treat Rev.* 2015;41(7):605-613. doi:10.1016/j.ctrv.2015.04.012
- Goh BC, Lee SC, Wang LZ, et al. Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies. *J Clin Oncol.* 2002;20(17):3683-3690. doi:10.1200/JCO.2002.01.025
- Yamamoto N, Tamura T, Murakami H, et al. Randomized pharmacokinetic and pharmacodynamic study of docetaxel: dosing based on body-surface area compared with individualized dosing based on cytochrome P450 activity estimated using a urinary metabolite of exogenous cortisol. *J Clin Oncol.* 2005;23(6):1061-1069. doi:10.1200/JCO.2005.11.036
- Rivory LP, Slaviero KA, Clarke SJ. Hepatic cytochrome P450 3A drug metabolism is reduced in cancer patients who have an acute-phase response. *Br J Cancer.* 2002;87(3):277-280. doi:10.1038/sj.bjc.6600448
- Krens SD, McLeod HL, Hertz DL. Pharmacogenetics, enzyme probes and therapeutic drug monitoring as potential tools for individualizing taxane therapy. *Pharmacogenomics.* 2013;14(5):555-574. doi:10.2217/pgs.13.33
- Andrigueti NB, Raymundo S, Antunes MV, et al. Pharmacogenetic and pharmacokinetic dose individualization of the taxane chemotherapeutic drugs paclitaxel and docetaxel. *Curr Med Chem.* 2017;24(33):3559-3582. doi:10.2174/0929867324666170623093445
- Veyrat-Follet C, Bruno R, Olivares R, Rhodes GR, Chaikin P. Clinical trial simulation of docetaxel in patients with cancer as a tool for dosage optimization. *Clin Pharmacol Ther.* 2000;68(6):677-687. doi:10.1067/mcp.2000.111948
- Harvey V, Mouridsen H, Semiglazov V, et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. *J Clin Oncol.* 2006;24(31):4963-4970. doi:10.1200/JCO.2005.05.0294
- Fr Brunsvig P, Andersen A, Aamdal S, Kristensen V, Olsen H. Pharmacokinetic analysis of two different docetaxel dose levels in patients with non-small cell lung cancer treated with docetaxel as monotherapy or with concurrent radiotherapy. *BMC Cancer.* 2007;23(7):197. doi:10.1186/1471-2407-7-197
- Eckmann K, Michaud LB, Rivera E, et al. Pilot study to assess toxicity and pharmacokinetics of docetaxel in patients with metastatic breast cancer and impaired liver function secondary to hepatic metastases. *J Oncol Pharm Pract.* 2014;20(2):120-129. doi:10.1177/1078155213480536
- Ozawa K, Minami H, Sato H. Logistic regression analysis for febrile neutropenia (FN) induced by docetaxel in Japanese cancer patients. *Cancer Chemother Pharmacol.* 2008;62(3):551-557. doi:10.1007/s00280-007-0648-8
- Baker S, Li J, Tentije A, et al. Relationship of systemic exposure to unbound docetaxel and neutropenia. *Clin Pharmacol Ther.* 2005;77(1):43-53. doi:10.1016/j.cpt.2004.09.005
- Engels FK, Loos WJ, van der Bol JM, et al. Therapeutic drug monitoring for the individualization of docetaxel dosing: a randomized pharmacokinetic study. *Clin Cancer Res.* 2011;17(2):353-362. doi:10.1158/1078-0432.CCR-10-1636
- Baker SD, Sparreboom A, Verweij J. Clinical pharmacokinetics of docetaxel: recent developments. *Clin Pharmacokinet.* 2006;45(3):235-252. doi:10.2165/00003088-200645030-00002
- Gerritsen-van Schieveen P, Royer B, Therapeutic drug monitoring group of the French Society of Pharmacology and Therapeutics. Level of evidence for therapeutic drug monitoring of taxanes. *Fundam Clin Pharmacol.* 2011;25(4):414-424. doi:10.1111/j.1472-8206.2010.00874.x

24. Willson ML, Burke L, Ferguson T, Ghersi D, Nowak AK, Wilcken N. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Syst Rev*. 2019;9(9):CD004421. doi:[10.1002/14651858.CD004421.pub3](https://doi.org/10.1002/14651858.CD004421.pub3)
25. Nieto Y, Aldaz A, Rifón J, et al. Phase I and pharmacokinetic study of gemcitabine administered at fixed-dose rate, combined with docetaxel/melphalan/carboplatin, with autologous hematopoietic progenitor-cell support, in patients with advanced refractory tumors. *Biol Blood Marrow Transplant*. 2007;13(11):1324-1337. doi:[10.1016/j.bbmt.2007.07.008](https://doi.org/10.1016/j.bbmt.2007.07.008)
26. López LZ, Pastor AA, Aramendia Beitia JM, Velilla JA, Deiró JG. Determination of docetaxel and Paclitaxel in human plasma by high-performance liquid chromatography: validation and application to clinical pharmacokinetic studies. *Ther Drug Monit*. 2006;28(2):199-205. doi:[10.1097/01.ftd.0000189903.46802.1f](https://doi.org/10.1097/01.ftd.0000189903.46802.1f)
27. Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. *Ther Drug Monit*. 2012;34(4):467-476. doi:[10.1097/FTD.0b013e31825c4ba6](https://doi.org/10.1097/FTD.0b013e31825c4ba6)
28. Bustad A, Terziyanov D, Leary R, Port R, Schumitzky A, Jelliffe R. Parametric and nonparametric population methods: their comparative performance in analysing a clinical data set and two monte carlo simulation studies. *Clin Pharmacokinet*. 2006;45(4):365-383. doi:[10.2165/00003088-200645040-00003](https://doi.org/10.2165/00003088-200645040-00003)
29. Roberts JK, Fan X. Bootstrapping within the multilevel/hierarchical linear modeling framework: a primer for use with SAS and SPLUS. *Multiple Linear Regression Viewpoints (MLRV)*. 2004;30(1):23-34.
30. Jelliffe RW, Schumitzky A, van Guilder M, et al. Individualizing drug dosage regimens: roles of population pharmacokinetic and dynamic models, Bayesian fitting, and adaptive control. *Ther Drug Monit*. 1993;15(5):380-393. doi:[10.1097/00007691-199310000-00005](https://doi.org/10.1097/00007691-199310000-00005)
31. Olivetto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. *J Clin Oncol*. 2005;23(12):2716-2725. doi:[10.1200/JCO.2005.06.178](https://doi.org/10.1200/JCO.2005.06.178)
32. Pérez-Pitarch A, Guglieri-López B, Nacher A, Merino V, Merino-Sanjuán M. Impact of undernutrition on the pharmacokinetics and pharmacodynamics of anticancer drugs: A literature review. *Nutr Cancer*. 2017;69(4):555-563. doi:[10.1080/01635581.2017.1299878](https://doi.org/10.1080/01635581.2017.1299878)
33. Wang L, Zhang S, Wang X. The metabolic mechanisms of breast cancer metastasis. *Front Oncol*. 2020;10:1-21. doi:[10.3389/fonc.2020.602416](https://doi.org/10.3389/fonc.2020.602416)
34. Baker S, Zhao M, Lee C, et al. Comparative pharmacokinetics of weekly and every-three weeks docetaxel. *Clin Cancer Res*. 2004;10(6):1976-1983. doi:[10.1158/1078-0432.CCR-0842-03](https://doi.org/10.1158/1078-0432.CCR-0842-03)
35. Minami H, Kawada K, Sasaki Y, et al. Pharmacokinetics and pharmacodynamics of protein-unbound docetaxel in cancer patients. *Cancer Sci*. 2006;97(3):235-241. doi:[10.1111/j.1349-7006.2006.00166.x](https://doi.org/10.1111/j.1349-7006.2006.00166.x)
36. Ma Y, Lin Q, Yang Y, et al. Clinical Pharmacokinetics and drug exposure-toxicity correlation study of docetaxel-based chemotherapy in Chinese head and neck cancer patients. *Ann Transl Med*. 2020;8(5):236-246. doi:[10.21037/atm.2020.01.76](https://doi.org/10.21037/atm.2020.01.76)
37. Ma Y, Zhao X, Chen X, et al. Therapeutic drug monitoring of docetaxel by pharmacokinetics and pharmacogenetics: a randomized clinical trial of AUC-guided dosing in non-small cell lung cancer. *Clin Transl Med*. 2021;11(4):e354. doi:[10.1002/ctm2.354](https://doi.org/10.1002/ctm2.354)
38. Slaviero KA, Clarke SJ, McLachlan AJ, Blair EYL, Rivory LP. Population pharmacokinetics of weekly docetaxel in patients with advanced cancer. *Br J Clin Pharmacol*. 2004;57(1):44-53. doi:[10.1046/j.1365-2125.2003.01956.x](https://doi.org/10.1046/j.1365-2125.2003.01956.x)
39. McLeod HL, Kearns CM, Kuhn JG, Bruno R. Evaluation of the linearity of docetaxel pharmacokinetics. *Cancer Chemother Pharmacol*. 1998;42(2):155-159. doi:[10.1007/s002800050799](https://doi.org/10.1007/s002800050799)
40. Semb KA, Aamdal S, Oian P. Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment. *J Clin Oncol*. 1998;16(10):3426-3432. doi:[10.1200/JCO.1998.16.10.3426](https://doi.org/10.1200/JCO.1998.16.10.3426)
41. ten Tije AJ, Verweij J, Carducci MA, et al. Prospective evaluation of the pharmacokinetics and toxicity profile of docetaxel in the elderly. *J Clin Oncol*. 2005;23(6):1070-1077. doi:[10.1200/JCO.2005.03.082](https://doi.org/10.1200/JCO.2005.03.082)
42. Engels FK, Verweij J. Docetaxel administration schedule: from fever to tears? A review of randomised studies. *Eur J Cancer*. 2005;41(8):1117-1126. doi:[10.1016/j.ejca.2005.02.016](https://doi.org/10.1016/j.ejca.2005.02.016)
43. Kuroi K, Bando H, Saji S, Toi M. Weekly schedule of docetaxel in breast cancer: evaluation of response and toxicity. *Breast Cancer*. 2003;10(1):10-14. doi:[10.1007/BF02967619](https://doi.org/10.1007/BF02967619)
44. Sandström M, Lindman H, Nygren P, Lidbrink E, Bergh J, Karlsson MO. Model describing the relationship between pharmacokinetics and hematologic toxicity of the epirubicin-docetaxel regimen in breast cancer patients. *J Clin Oncol*. 2005;23(3):413-421. doi:[10.1200/JCO.2005.09.161](https://doi.org/10.1200/JCO.2005.09.161)
45. Bruno R, Vivier N, Veyrat-Follet C, Montay G, Rhodes GR. Population pharmacokinetics and pharmacokinetic-pharmacodynamic relationships for docetaxel. *Invest New Drugs*. 2001;19(2):163-169. doi:[10.1023/a:1010687017717.40](https://doi.org/10.1023/a:1010687017717.40)
46. Puisset F, Alexandre J, Treluyer J, et al. Clinical pharmacodynamics factors in docetaxel toxicity. *Br J Cancer*. 2007;97(3):290-296. doi:[10.1038/sj.bjc.6603872](https://doi.org/10.1038/sj.bjc.6603872)
47. Hudis CA, Seidman AD, Crown JP, et al. Phase II and pharmacologic study of docetaxel as initial chemotherapy for metastatic breast cancer. *J Clin Oncol*. 1996;14(1):58-65. doi:[10.1200/JCO.1996.14.1.58](https://doi.org/10.1200/JCO.1996.14.1.58)
48. Pinto L, Liu Z, Doan Q, Bernal M, Dubois R, Lyman G. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. *Curr Med Res Opin*. 2007;23(9):2283-2295. doi:[10.1185/030079907X219599](https://doi.org/10.1185/030079907X219599)
49. Alexander S, Minton O, Andrews P, Stone P. A comparison of the characteristics of disease-free breast cancer survivors with or without cancer-related fatigue syndrome. *Eur J Cancer*. 2009;45(3):384-392. doi:[10.1016/j.ejca.2008.09.010](https://doi.org/10.1016/j.ejca.2008.09.010)

## SUPPORTING INFORMATION

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