PERGAMON

European Journal of Cancer 39 (2003) 196–202

European Journal of Cancer

www.ejconline.com

Altered clearance of unbound paclitaxel in elderly patients with metastatic breast cancer

C. H. Smorenburg[a], A. J. ten Tije[a], J. Verweij[a], M. Bontenbal[a], K. Mross[b], D. M. van Zomeren[a], C. Seynaeve[a], A. Sparreboom[a,*]

[a]*Department of Medical Oncology, Erasmus MC—Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands*
[b]*Department of Medical Oncology and Clinical Pharmacology, Albert-Ludwigs-University Freiburg, 79106 Freiburg im Breisgau, Germany*

Received 2 April 2002; received in revised form 16 August 2002; accepted 4 October 2002

Abstract

The pharmacokinetic behaviour of anticancer drugs may be altered with aging due to (for example) differences in body composition and decreased hepatic and renal function. To address this issue for paclitaxel, we studied the pharmacokinetics of the drug in eight elderly women ($\geqslant 70$ years) with metastatic breast cancer (median age (range), 77 years (70–84 years)) and a control group of 15 patients aged <70 years (median age (range), 54 years (22—69 years)). Paclitaxel was administered as a 1-h intravenous (i.v.) infusion at a dose of 80 (elderly) or 100 mg/m^2 (<70 years), and serial blood samples were obtained at baseline, and up to 24 h after the end of infusion. Paclitaxel concentration–time profiles were fitted to a linear three-compartment model without any demonstration of saturable behaviour. The clearance of unbound paclitaxel was 124 ± 35.0 (elderly) versus 247 ± 55.4 l/h/m^2 (<70 years) ($P = 0.002$), and was inversely related to the patient's age ($R^2 = 0.857$; $P < 0.00001$). Total plasma clearance of the formulation vehicle Cremophor EL (CrEL) was 150 ± 60.7 (elderly) versus 115 ± 39.2 ml/h/m^2 (<70 years) ($P = 0.04$). These data indicate an approximately 50% change in total body clearance of unbound paclitaxel and a concomitant significant increase in systemic exposure with age, most likely as a result of altered CrEL disposition. The clinical relevance of these observations with respect to toxicity profiles and antitumour efficacy requires further evaluation.

Keywords: Paclitaxel; Elderly patients; Breast cancer; Pharmacokinetics; Pharmacology

1. Introduction

As the incidence of breast cancer rises with advancing age, and populations in Western countries are aging, the total number of women with breast cancer will increase substantially [1]. Unfortunately, elderly patients are still underrepresented in trials on cancer therapies, especially on breast cancer treatment [2]. This holds true even after the exclusion of trials restricted to patients younger than 65 years [2]. Moreover, as elderly patients frequently suffer from impaired organ functions and/or comorbidity, extrapolating standard recommendations for chemotherapy in metastatic breast cancer patients to the elderly might result in excessive toxicity [3]. Notwithstanding the large number of elderly patients, and the known impact of impaired renal and hepatic functions on the absorption, distribution, metabolism and excretion of various anticancer agents, including taxanes, there have been only a few pharmacological studies conducted in this subgroup of patients [4].

The cytotoxic agent paclitaxel (Taxol) is registered for the treatment of advanced breast cancer, for which it is usually administered in second-line therapy as a single agent every 3 weeks at a dose of 175–225 mg/m^2. Frequently encountered side-effects are neutropenia, neuropathy, asthenia and alopecia. Weekly administration of paclitaxel has demonstrated sustained efficacy together with a more favourable toxicity profile lacking severe myelotoxicity [5]. While the related agent docetaxel, despite a dose reduction of 75% of the standard dose of 100 mg/m^2 every 3 weeks, appeared to be too toxic in non-pretreated patients aged >70 years with metastatic breast cancer, a weekly schedule at a dose of 36 mg/m^2 in heavily pretreated elderly patients indeed

* Corresponding author. Present address: Clinical Pharmacology Research Core, Medical Oncology Clinical Research Unit, Center for Cancer Research, National Cancer Institute/National Institute of Health, Building 10, Room 5A01, MSC1910, 9000 Rockville Pike, Bethesda, MD 20892, USA. Tel.: +1-301-402-3623; fax: +1-301-402-8606.

0959-8049/03/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0959-8049(02)00611-1

appeared effective and well tolerated [6–8]. Recently published data suggest similar efficacy for weekly paclitaxel [9,10]. This way of administering paclitaxel therefore seems an attractive chemotherapeutic alternative for elderly women with metastatic breast cancer, although no pharmacological data are yet available. Here, we studied the pharmacokinetics of paclitaxel and its formulation vehicle Cremophor EL (CrEL) in patients with breast cancer aged $\geqslant 70$ years treated in a weekly schedule, and compared the results with a control group of patients aged <70 years treated in a similar way.

2. Patients and methods

2.1. Eligibility criteria

Two groups of patients were studied based on age; patients aged $\geqslant 70$ years were eligible if they had histologically or cytologically confirmed breast cancer, unresponsive to hormonal therapy, while patients aged between 18 and 70 years were eligible if they had any histologically or cytologically confirmed metastatic solid tumour for which treatment with paclitaxel was a viable option. Prior to recruiting male patients in the control group, it was confirmed that there are no sex-related differences in unbound paclitaxel clearance. This was investigated in unpublished data from a historical patient population treated at the Erasmus MC—Daniel den Hoed Cancer Center (Rotterdam, The Netherlands) with single agent paclitaxel given as a 1-h intravenous (i.v.) infusion at dose levels ranging between 70 and 200 mg/m^2. The group consisted of 10 males (median age, 58 years; range 46–70 years) and 30 females (median age, 57 years; range 29–71 years). The mean ($\pm$standard deviation (S.D.)) values for clearance of unbound paclitaxel in male and female patients were 200 ± 35.6 and 195 ± 48.3 l/h/m^2, respectively, which is a not statistically significant difference ($P = 0.75$; mean difference ($\pm$standard error of the mean (S.E.), 5.26 ± 16.3 l/h/m^2; 95% confidence limits for the mean difference, -27.8 and 38.3; unpaired two-tailed Student's t-test).

Other criteria for patient enrollment were (i) acceptable performance status according to the World Health Organization criteria (WHO) (0–2), (ii) an adequate bone marrow function (defined by pretherapy values of haemoglobin $\geqslant 6.0$ mM, absolute neutrophil count (ANC) $>1.5\times10^9$/l, and platelet count $>160\times10^9$/l), (iii) adequate renal function (creatinine levels <175 μM) and (iv) adequate hepatic function (bilirubin levels <25 μM). Patients with other malignancies during the past 5 years, neuropathy graded $\geqslant 2$, symptomatic cardiac disease, and/or signs of central nervous system involvement were excluded. All patients gave written informed consent, and the study protocol was reviewed and approved by the Erasmus MC—Daniel den Hoed Cancer Center review board (Rotterdam, The Netherlands).

2.2. Treatment schedule and patient evaluation

Paclitaxel was administered as a 1-h i.v. infusion at a dose of 80 mg/m^2 (elderly patients) or 100 mg/m^2 (those aged <70 years) on days 1, 8 and 15 with treatment cycles repeated every 4 weeks until progressive disease or the occurrence of serious treatment-related side-effects. All premedication, consisting of dexamethasone (10 mg), clemastine (2 mg) and ranitidine (50 mg), was administered by the i.v. route at 30 min prior to paclitaxel infusion. Pretreatment evaluation consisted of a complete history and physical examination, complete blood cell counts, serum chemistry analysis, electrocardiogram, chest X-ray. Complete blood cell counts were measured on a weekly basis, while other tests were repeated before the next full cycle. Toxicity in each patient following paclitaxel administration was evaluated using the National Cancer Institute common toxicity criteria (NCI CTC) version 2.0.

2.3. Pharmacokinetic and pharmacodynamic analysis

Blood samples for pharmacokinetic analysis were collected from all patients only on day 1 of the first administration from a vein in the arm opposite to the one used for drug infusion. Blood samples of 5 ml were obtained at the following time points: before infusion, at 0.5 h after the start of infusion, 5 min before the end of infusion, and at 5, 15, 30 min and 1, 2, 4, 8, 12 and 24 h after the end of infusion. Samples were collected in tubes containing lithium heparin as an anticoagulant and were subsequently centrifuged at 3000g for 10 min at 4 °C to separate the plasma and cells. Plasma samples were stored frozen at -80 °C until analysis.

In view of the profound non-linear disposition of paclitaxel in patients [11], the pharmacological consequences of the treatment in patients with increasing age can not be predicted based on total plasma levels alone when different dose groups are compared. Since the area under the plasma concentration–time curve (AUC) of unbound paclitaxel is a linear function of the dose administered [12,13], we focused here on comparing the fraction of unbound paclitaxel between the two groups. Concentrations of total paclitaxel in plasma samples were determined by a validated reversed-phase high-performance liquid chromatography with ultraviolet detection as described earlier in Ref. [14]. The free drug fraction of paclitaxel was measured by using a reproducible equilibrium dialysis method using a tritiated-paclitaxel tracer [12]. Coinciding levels of CrEL were measured by a colorimetric dye-binding microassay, as published in Ref. [15]. The kinetics of paclitaxel

and CrEL were evaluated for each patient separately by a linear three-compartment model and by model-independent methods, respectively, using the Siphar version 4.0 software package (InnaPhase, Philadelphia, PA, USA). This program determines the slopes and intercepts of the logarithmically plotted curves of multi-exponential functions using non-linear least-squares, iterative steps. Initial parameter estimates were determined by an automated curve-stripping procedure. The mathematical equations describing the drug concentration $C_{(t)}$ at any time t during (Eq. (1)) and after i.v. administration (Eq. (2)) are given by:

$$C_{(t)} = \Sigma\left\{C_i/(\lambda_i \times T_{\text{inf}}) \times \left(1 - e^{(-\lambda_i \times t)}\right)\right\} \quad (1)$$

$$C_{(t)} = \Sigma\left\{C_i/(\lambda_i \times T_{\text{inf}}) \times \left(e^{(-\lambda_i \times [t - T_{\text{inf}}])} - e^{(-\lambda_i \times t)}\right)\right\} \quad (2)$$

In these equations, λ_i is the component of the ith exponential term, C_i is the initial concentration of the ith component of the curve, and T_{inf} is the infusion duration. In all cases, paclitaxel-concentration–time curves were best described with a tri-exponential model, which gave the lowest Akaike information criterion, without any demonstration of saturable behaviour ($R^2 = 0.996 \pm 0.002$, root mean square error = $13.5 \pm 3.53\%$). The curve fitting procedure with this model yields the parameters C_1, C_2, C_3, λ_1, λ_2 and λ_3. The AUC values were determined on the basis of the parameters of Eqs. (1) and (2) with extrapolation to infinity using the terminal disposition rate constant. The clearance was defined as dose (expressed in μmol/m^2) divided by AUC. The volume of distribution at steady-state was calculated as the product of clearance and the mean residence time, also estimated from Eqs. (1) and (2). Peak plasma concentrations were put on par with observed (experimental) drug levels immediately following the end of infusion. The fraction unbound paclitaxel was defined as the ratio of unbound paclitaxel AUC and total paclitaxel AUC. Pharmacodynamics was assessed by calculation of the relative haematological toxicity of white blood cell count (WBC) and absolute neutrophil count (ANC), defined as:

$$\%\text{decrease} = [(\text{pretherapy value} - \text{nadir value})/(\text{pretherapy value})] \times 100\% \quad (3)$$

2.4. Statistical evaluation

All pharmacological parameters are expressed as mean values ± S.D. Differences in any of the studied pharmacokinetic and pharmacodynamic parameters between the two age groups or within the control group between male and female patients were evaluated statistically using an unpaired two-tailed Student's t-test after testing for normality. The relationship between clearance of unbound paclitaxel and age was evaluated using least-squares linear regression analysis and adjusted R^2 values to compensate for the expected chance prediction when the null hypothesis is true. The level of significance was set at $P < 0.05$. All statistical calculations were performed using Number Cruncher Statistical System v5.X (Jerry Hintze, Kaysville, UT, USA).

3. Results

3.1. Patient characteristics

A total of 8 elderly patients and 15 patients aged <70 years was studied (Table 1), and all were evaluable for paclitaxel pharmacokinetics and toxicity. The median age in the groups was 77 years (range 70–84 years) and 54 years (range 22–69 years), respectively. Other patient characteristics and baseline clinical chemistry values were similar between the two groups (Table 1). In the elderly group, 7 of 8 patients had received prior hormonal therapy for metastatic disease, and a median number of four cycles (range, 1–6 cycles) was administered per patient.

3.2. Pharmacokinetics

Unbound paclitaxel concentration–time curves for both groups are shown in Fig. 1. Overall, the inter-patient variability in unbound paclitaxel clearance was moderate (coefficient of variation, 30.8%). A summary of pharmacokinetic data of unbound paclitaxel, total paclitaxel and CrEL is shown in Table 2. In the control group, there were no significant sex-related differences in unbound paclitaxel clearance (males versus females, 251 ± 74.3 versus 237 ± 43.0 l/h/m^2; $P = 0.67$), total paclitaxel clearance (18.4 ± 5.63 versus 16.6 ± 2.69 l/h/m^2; $P = 0.43$), the fraction unbound paclitaxel

Table 1
Patient characteristics and baseline clinical chemistry values (median with range)

Characteristic	Patients ⩾70 years	Patients <70 years
No. studied	8	15
Age (years)	77 (70–84)	54 (22–69)
BSA (m^2)	1.75 (1.45–1.91)	1.76 (1.31–2.37)
Weight (kg)	71.6 (54.0–84.3)	68.1 (36.6–116)
Height (cm)	160 (150–167)	165 (157–185)
Sex (M/F)	0/8	7/8
Serum albumin (g/l)	42 (38–47)	38 (24–47)
Total serum protein (g/l)	74 (69–80)	69 (49–79)
Haematocrit (l/l)	0.35 (0.27–0.40)	0.35 (0.29–0.44)

BSA, body-surface area; M, male; F, female.

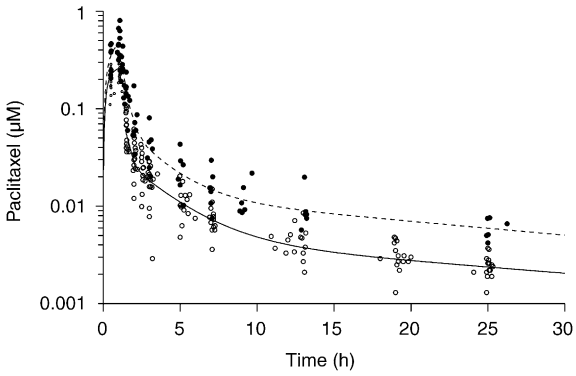

Fig. 1. Plasma concentration-time profiles of unbound paclitaxel in elderly (⩾70 years) patients ($n=8$; closed symbols and dotted line) and patients <70 years ($n=15$; open symbols and solid line) receiving a 1-h intravenous (i.v.) infusion of paclitaxel at a dose levels of 80 and 100 mg/m^2, respectively. Data from the elderly group were normalised to a paclitaxel dose of 100 mg/m^2, by multiplying unbound paclitaxel concentrations (Cu) by the dose difference (Cu×(100/80)). The mathematical equations describing the drug concentration ($C_{(t)}$) at any time (t) during (Eq. (1)) and after i.v. administration (Eq. (2)) are given by: $C_{(t)}=\Sigma\{C_i/(\lambda_i\times T_{inf})\times(1-e^{(-\lambda i\times t)})\}$ (Eq. (1)) and $C_{(t)}=\Sigma\ \{C_i/(\lambda_i\times T_{inf})\times(e^{(-\lambda i\times[t-T_{inf}])}-e^{(-\lambda i\times t)})\}$ (Eq. (2)). The model parameters were $C_1=1.19$ μM, $C_2=0.076$ μM $C_3=0.013$ μM, $\lambda_1=2.96$ h^{-1}, $\lambda_2=0.444$ h^{-1} and $\lambda_3=0.033$ h^{-1} for the elderly patients, and $C_1=0.976$ μM, $C_2=0.033$ μM, $C_3=0.005$ μM, $\lambda_1=4.26$ h^{-1}, $\lambda_2=0.350$ h^{-1} and $\lambda_3=0.029$ h^{-1} for the younger patients.

Table 2
Summary of paclitaxel and CrEL pharmacokinetics (mean±S.D.)

Parameter	Patients ⩾70 years	Patients <70 years
No. of patients	8	15
Paclitaxel dose		
(mg/m^2)	80	100
(mg)[a]	140 (105–170)	170 (130–226)
Infusion duration (h)[a]	1.00 (0.90–1.21)	1.00 (0.98–1.19)
Unbound paclitaxel		
C_{max} (μM)	0.366±0.155	0.262±0.079
AUC (μM·h)	0.749±0.231	0.503±0.095
CL (l/h/m^2)	124±35.0	247±55.4*
V_{ss} (l/m^2)	1105±300	2546±754**
$T_{1/2}$ (h)	18.0±7.40	21.7±4.33
fu	0.095±0.014	0.085±0.006
Total paclitaxel		
C_{max} (μM)	3.22±1.30	3.37±0.730
AUC (μM·h)	6.92±1.25	5.99±1.12
CL (l/h/m^2)	13.9±2.31	17.4±4.52***
CrEL		
C_{max} (μl/ml)	2.51±0.34	2.82±0.76
AUC (μl·h/ml)	51.8±22.0	80.2±27.3
CL (ml/h/m^2)	150±60.7	115±39.2****

C_{max}, peak plasma concentration; AUC, area under the plasma concentration–time curve; CL, plasma clearance; $T_{1/2}$, half-life of the terminal disposition phase; fu, unbound drug fraction (AUC unbound drug/AUC total drug); S.D., standard deviation; V_{SS}, volume of distribution at steady state.

[a] Median with range. *$P=0.002$; **$P<0.001$; ***$P=0.04$; ****$P=0.04$.

(0.084±0.007 versus 0.085±0.005; $P=0.76$), and the clearance of CrEL (115±41.7 versus 114±39.2 ml/h/m^2; $P=0.94$). Therefore, pharmacokinetic data were directly compared between the groups despite the distribution of males and females being unequally represented in the elderly and younger patient groups.

The clearances of unbound paclitaxel and total paclitaxel were significantly different between the two age groups, with mean values (elderly versus younger) of 124±35.0 versus 247±55.4 l/h/m^2 ($P=0.002$) and 13.9±2.31 versus 17.4±4.52 l/h/m^2 ($P=0.04$), respectively (Table 2). The difference in unbound paclitaxel clearance remained significant when the eight females in the elderly group were compared with the eight females in the control group (124±35.0 versus 237±43.0 l/h/m^2; $P=0.002$). In the entire patient population, a significant negative correlation was observed between age and unbound paclitaxel clearance (Fig. 2; clearance (in l/h/m^2) = (−4.127×age) + 457.5; adjusted $R^2=0.847$; $P<0.00001$). The unbound paclitaxel volume of distribution at steady state was also significantly smaller in the elderly patients (1105±300 versus 2546±754 l/m^2; $P<0.001$), whereas the terminal disposition half-life was similar (18.0±7.40 versus 21.7±4.33 h; $P=0.14$). The clearance of CrEL was significantly faster in the elderly patients compared with the control group (150±60.7 versus 115±39.2 ml/h/m^2; $P=0.04$).

3.3. Toxicity profiles

Only four administrations (5%) were delayed, of which one was due to erysipelas and three were due to non-therapy-related morbidity. Dose reductions were not required in any patient from both groups, and no cumulative toxicity of any kind was seen. In the elderly group grade 2 fatigue was common, in line with previous findings [16], and resulted in the discontinuation of treatment in 2 patients. One patient experienced a grade 3 toxicity (neutropenia and skin toxicity with generalized erythroderma), while no grade 3 or 4 toxi-

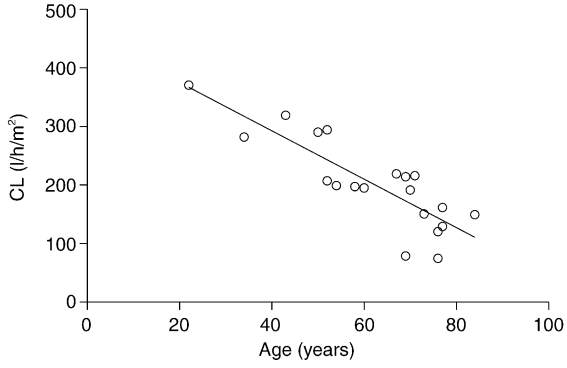

Fig. 2. Relationship between patient age and unbound paclitaxel clearance (CL). The solid line indicates the fit of a least-squares linear regression analysis ((CL) = (−4.127×age) + 457.5; adjusted $R^2=0.847$; $P<0.00001$).

cities were noted in any of the other patients. In spite of the difference in the paclitaxel dose administered, no significant difference was observed in haematological pharmacodynamics between the two groups as defined by the percent decrease in white blood cells (WBC) (40.7 ± 7.96 versus $45.9 \pm 15.5\%$; $P = 0.39$) and the percent decrease in ANC (50.8 ± 14.6 versus $56.3 \pm 14.8\%$; $P = 0.40$). This is consistent with the increased exposure to paclitaxel in the group of elderly patients.

4. Discussion

In the present study, we have described for the first time the pharmacokinetics of unbound paclitaxel in cancer patients as a function of age. Overall, our data indicate that the clearance of unbound paclitaxel, following weekly administration as a 1-h i.v. infusion, is approximately 50% reduced in elderly patients ($\geqslant 70$ years) compared with younger patients, and that age is a significant predictor of paclitaxel disposition in the population studied. These data complement previous knowledge on the clinical pharmacology of paclitaxel, and may have important practical implications for its optimal use. Indeed, while some studies have examined the efficacy and feasibility of chemotherapy in elderly patients with metastatic breast cancer, little is known about the pharmacokinetic behaviour of the anticancer agents involved, with the notable exception of some anthracyclines and *Vinca* alkaloids [4]. For doxorubicin, a trend for delayed clearance in elderly cancer patients has been documented, while the AUC of daunorubicinol, an active metabolite of daunorubicin, was significantly increased in 13 elderly patients with acute leukaemia [17,18]. In patients aged $\geqslant 70$ years, the clearance of vinorelbine was reduced by 30–40%, compared with adult patients [19]. To adjust for decreasing renal function with age, a study investigating combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil in women aged $\geqslant 65$ years used creatinine clearance for calculation of appropriate doses of cyclophosphamide and methotrexate [20]. While indeed less toxicity resulted, unfortunately no pharmacokinetic analysis was performed.

For paclitaxel, only scarce data are available on the effect of aging on the agent's pharmacokinetic behaviour. Nakamura and colleagues performed a retrospective analysis investigating total paclitaxel pharmacokinetics in 120 lung cancer patients, of whom 28 were elderly, treated at a dose of 210 mg/m^2 given over 3 h in a 3-weekly regimen [21]. These authors could not detect any differences in AUC, peak concentration, terminal disposition half-life, and time above the threshold of 0.1 μM between patients aged <70 years and those >70 years [21]. Likewise, Fidias and colleagues recently reported that the clearance of total paclitaxel in a group of 8 patients with non-small cell lung cancer (age $\geqslant 70$ years) treated with a dose of 90 mg/m^3 as a 1-h i.v. infusion was comparable to values that have been reported for studies involving younger patients [22]. However, these apparent inconsistencies with our current findings need to be interpreted with great caution as, in the study performed by Fidias and colleagues, no control group involving younger patients was studied, and a host of confounding factors might influence their overall conclusions, including differences in the paclitaxel dose administered between the comparative trials, variability in analytical methods employed, and parameter calculation procedure used. In contrast to conclusions drawn in the above studies [21,22], Lichtman and colleagues recently reported in abstract form a significant difference in AUC and clearance of total paclitaxel with advancing age in 113 patients treated with paclitaxel at a dose of 175 mg/m^2 administered as a 3-h infusion [23]. The total paclitaxel clearances in patients aged 55–64 years and in 28 patients >75 years were 10.9 and 8.21 l/h/m^2, respectively, which was significant at $P = 0.012$. Unfortunately, these investigators used a strategy for AUC calculation based on the use of only a few timed samples early (i.e. a limited-sampling strategy) up to 7 h after dosing, which may have caused a serious flaw in that any alteration in drug elimination as a result of aging (e.g. metabolic and excretory routes) may remain undetected by such methodology. Moreover, as it cannot be excluded that any alteration in paclitaxel disposition is (partially) associated with changes in CrEL pharmacokinetics as a function of age (see below), the use of total plasma concentrations and subsequent calculation of total plasma clearance, as was done in the mentioned studies [21–23], may be essentially less meaningful. The results of the various investigations performed to date further emphasise the need to simultaneously study paclitaxel pharmacokinetics in a control group of younger patients when evaluating the role of patient age in drug disposition.

Previous investigations have demonstrated the importance of unbound paclitaxel AUC as a pharmacokinetic parameter to delineate exposure–toxicity relationships, both with 1- and 3-h infusion schedules [13,24]. Although intuitively the unbound fraction of paclitaxel accounts for the (cyto)toxic actions of the treatment, its concentration has never been investigated in elderly patients. We have recently shown that CrEL, the vehicle used for i.v. paclitaxel administration, has a substantial impact on the fraction unbound paclitaxel [25,26]. Although the exact mechanism underlying this interaction has not yet been fully elucidated, the presence of CrEL in the circulation as large polar micelles is thought to entrap paclitaxel, thereby reducing cellular accumulation of paclitaxel in blood cells (e.g. erythrocytes) and altering the fraction of unbound paclitaxel in whole blood. Since CrEL clearance increases

with prolonged duration of infusion from 1- to 3- and 24-h, the systemic exposure to unbound paclitaxel and CrEL significantly depends on the duration of drug infusion [27]. Our current data on unbound paclitaxel levels in elderly patients should therefore not be compared with studies using other infusion schedules. In any event, the demonstration that CrEL clearance is significantly increased by 30% in elderly patients, combined with the notion that CrEL micelles act as the principal carrier of paclitaxel in the systemic circulation [28], suggests that this phenomenon likely contributes substantially to the changes in unbound paclitaxel clearance.

The mechanisms underlying the age-dependent pharmacokinetics of CrEL are not clear. In fact, the faster clearance of CrEL in the group of elderly patients is rather unusual, because for most xenobiotics that exhibit age-dependent pharmacokinetics, clearance tends to decrease with advancing age [29]. It has been previously shown that elimination routes of polyoxyethylated surfactants like CrEL are associated with esterase-mediated metabolic breakdown within the systemic circulation [26]. One possibility to explain the age-dependent pharmacokinetics of CrEL would be that CrEL biotransformation takes place at an accelerated rate as a result of elevated enzyme levels in the systemic circulation in elderly patients. This would be consistent with the observation that the clearance of CrEL is significantly higher (approximately 3- to 4-fold) in adult patients with moderate to severe hepatic dysfunction compared with patients with normal hepatic function [30]. This and several other possibilities, including diminished liver volume and blood flow [31], are currently under investigation.

As paclitaxel elimination is almost entirely caused by metabolic breakdown through cytochrome P450 (CYP) isoforms 3A4 and 2C8 [32], an alternative explanation for the altered paclitaxel clearance is an impaired hepatic function with advancing age. Although eligibility criteria excluded patients with an elevated bilirubin and all patients entered had normal values of aspartate and alanine aminotransferases, these laboratory values do not represent the actual capacity of hepatic metabolism [33]. A previous investigation in a group of 226 patients with equal histopathological conditions has shown a significant decline in total CYP content with age and a concomitant approximately 30% reduction of drug metabolism in patients after 70 years of age [34]. Thus, one possibility to investigate the role of altered liver function in relation to the current findings would be to determine pretreatment CYP3A4 and CYP2C8 activity in each patient using a functional surrogate such as the erythromycin breath test [35]. Additional clinical and pharmacological information is currently being collected by the implementation of such assays in ongoing trials with paclitaxel as well as docetaxel to further explore the role of enzyme capacity in taxane disposition in elderly patients.

Collectively, our study demonstrates that CrEL and unbound paclitaxel clearance are subject to considerable changes depending on age. In our patient population, haematological toxicity was relatively mild and not clinically relevant due to the low paclitaxel doses, precluding detection of statistically significant differences between both age groups. More insight will be provided by the ongoing Cancer Leukaemia Group B (CALGB) 9762 study, evaluating paclitaxel pharmacology in relation to patient age with drug administration over 3 h in a 3-weekly schedule at higher doses [23]. As the unbound fraction of paclitaxel is responsible for its cellular actions and its clearance is remarkably reduced in the elderly, this observation warrants further studies on the efficacy and feasibility of paclitaxel in aged patients using dose-dense regimens.

References

1. De Rijke JM, Schouten LJ, Hillen HFP, *et al*. Cancer in the very elderly dutch population. *Cancer* 2000, **89**, 1121–1133.
2. Hutchins LF, Unger JM, Crowley JJ, *et al*. Under-representation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999, **341**, 2061–2067.
3. Yancik R, Wesley MN, Ries LAG, *et al*. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *J Am Med Assoc* 2001, **285**, 885–892.
4. Balducci L, Parker M, Sexton W, Tantranond P. Pharmacology of antineoplastic agents in the elderly patients. *Semin Oncol* 1989, **16**, 76–84.
5. Seidman A, Hudis CA, Albanel J, *et al*. Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* 1998, **16**, 3353–3361.
6. Zanetta S, Albrand G, Bachelot T, *et al*. A phase I trial of docetaxel every 21 days in elderly patients with metastatic breast cancer. *Ann Oncol* 2000, **11**, 73 (abstr).
7. D'Hondt R, Paridaens R, Wildiers J, *et al*. Weekly docetaxel in aged or frail metastatic breast cancer patients: toxicity profile and activity. *Ann Oncol* 2000, **11**, 72 (abstr).
8. Hainsworth JD, Burris HA, Yardi DA, *et al*. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol* 2001, **19**, 3500–3505.
9. Repetto L, Pietropaolo M, Granata R, Ventura R, Gianni W. Weekly paclitaxel infusion in elderly patients with solid tumors. *Tumori* 2002, **88**, S39–S40.
10. Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Weekly paclitaxel in women age 65 and above with metastatic breast cancer. *Breast Cancer Res Treat* 2002, **73**, 85–88.
11. Kearns CM, Gianni L, Egorin MJ. Paclitaxel pharmacokinetics and pharmacodynamics. *Semin Oncol* 1995, **22**, 16–23.
12. Brouwer E, Verweij J, De Bruijn P, *et al*. Measurement of fraction unbound paclitaxel in human plasma. *Drug Metab Dispos* 2000, **28**, 1141–1145.
13. Henningsson A, Karlsson MO, Vigano L, *et al*. Mechanism-based pharmacokinetic model for paclitaxel. *J Clin Oncol* 2001, **19**, 4065–4073.
14. Sparreboom A, De Bruijn P, Nooter K, *et al*. Determination of paclitaxel in human plasma using single solvent extraction prior to isocratic reversed-phase high-performance liquid chromato-

graphy with ultraviolet detection. *J Chromatogr B* 1998, **705**, 159–164.
15. Sparreboom A, Loos WJ, Verweij J, *et al*. Quantitation of Cremophor EL in human plasma samples using a colorimetric dye-binding microassay. *Anal Biochem* 1998, **255**, 171–175.
16. Kouroussis C, Kakolyris S, Mavroudis D, *et al*. A dose-finding study of the weekly administration of paclitaxel in patients with advanced solid tumors. *Am J Clin Oncol* 2002, **24**, 404–407.
17. Egorin MJ, Zuhowski EG, Thompson B, *et al*. Age-related alterations in daunorubicin pharmacokinetics. *Proc Am Soc Clin Oncol* 1987, **6**, 38 (abstr).
18. Robert J, Hoerni J. Age dependence of the early-phase pharmacokinetics of doxorubicin. *Cancer Res* 1983, **43**, 4467–4469.
19. Gauvin A, Pinguet F, Culine S, *et al*. Bayesian estimate of vinorelbine pharmacokinetic parameters in elderly patients with advanced metastatic cancer. *Clin Cancer Res* 2000, **6**, 2690–2695.
20. Gelman R, Taylor SG. Cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: the elimination of age trends in toxicity by using doses based on creatinine clearance. *J Clin Oncol* 1984, **2**, 1404–1413.
21. 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**, 114–118.
22. Fidias P, Supko JG, Martins R, *et al*. A phase II study of weekly paclitaxel in elderly patients with advanced non-small cell lung cancer. *Clin Cancer Res* 2001, **7**, 3942–3949.
23. Lichtman SM, Egorin M, Rosner GL, *et al*. Clinical pharmacology of paclitaxel in relation to patient age: CALGB 9762. *Proc Am Soc Clin Oncol* 2001, **20**, 67a (abstr).
24. Gelderblom H, Mross K, Ten Tije AJ, *et al*. Comparative pharmacokinetics of unbound paclitaxel during 1- and 3-hour infusions. *J Clin Oncol* 2001, **20**, 574–581.
25. Sparreboom A, Van Zuylen L, Brouwer E. Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. *Cancer Res* 1999, **59**, 1454–1457.
26. Van Zuylen L, Verweij J, Sparreboom A. Role of formulation vehicles in taxane pharmacology. *Invest N Drugs* 2001, **19**, 125–141.
27. Van Zuylen L, Karlsson MO, Verweij J, *et al*. Pharmacokinetic modeling of paclitaxel encapsulation in Cremophor EL micelles. *Cancer Chemother Pharmacol* 2001, **47**, 309–318.
28. Van Zuylen L, Gianni L, Verweij J, *et al*. Interrelationships of paclitaxel disposition, infusion duration and Cremophor EL kinetics in cancer patients. *Anticancer Drugs* 2000, **11**, 331–337.
29. Kinirons MT, Crome P. Clinical pharmacokinetic considerations in the elderly. An update. *Clin Pharmacokin* 1997, **33**, 302–312.
30. Nannan Panday VR, Huizing MT, Van Tellingen O, *et al*. Pharmacologic study of Cremophor EL in cancer patients with impaired hepatic function receiving Taxol. In Nannan Panday V, ed. Clinical Pharmacology of Paclitaxel and Platinum Compounds, Thesis, Utrecht University, Utrecht, The Netherlands, 1998, 109–120.
31. Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. *Drugs Aging* 2001, **18**, 837–851.
32. Rahman A, Korzekwa KR, Grohan J, *et al*. Selective biotransformation of taxol to 6 alpha-hydroxytaxol by human cytochrome P450 2C8. *Cancer Res* 1994, **54**, 5543–5546.
33. Stewart CF, Schuetz EG. Need and potential for predictive tests of hepatic metabolism of anticancer drugs. *Clin Cancer Res* 2000, **6**, 3391–3392.
34. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther* 1997, **61**, 331–339.
35. Rivory LP, Slaviero KA, Hoskins JM, Clarke SJ. The erythromycin breath test for the prediction of drug clearance. *Clin Pharmacokin* 2001, **40**, 151–158.