Influence of Smoking on the Pharmacokinetics and Toxicity Profiles of Taxane Therapy

Anne-Joy M. de Graan¹, Walter J. Loos¹, Lena E. Friberg³, Sharyn D. Baker⁴, Jessica M. van der Bol¹, Leni van Doom¹, Erik A.C. Wiemer¹, Bronno van der Holt², Jaap Verweij¹, and Ron H.J. Mathijssen¹

Abstract

Purpose: Cigarette smoke is known to interact with the metabolism of several anticancer drugs. It may also affect the incidence and severity of adverse events and efficacy of chemotherapy. The main objective of this study was to examine the effects of smoking on the pharmacokinetics and toxicities of patients treated with docetaxel or paclitaxel.

Experimental Design: Smoking status, toxicity profiles, and pharmacokinetic parameters (calculated by nonlinear mixed-effect modeling population analysis) were determined in 566 patients (429 nonsmokers and 137 smokers) treated with docetaxel or paclitaxel.

Results: Smokers treated with docetaxel showed less grade IV neutropenia (35% vs. 52%; P = 0.01) than nonsmokers. Smokers treated with paclitaxel had less grade III–IV leukopenia than nonsmokers (12% vs. 25%; P = 0.03), and the white blood cell (WBC) nadir was lower in nonsmokers (median, 2.7 × 10⁹/L; range, 0.05 × 10⁹ to 11.6 × 10⁹/L) than in smokers (median, 3.3 × 10⁹/L; range 0.8 × 10⁹ to 10.2 × 10⁹/L; P = 0.02). Of interest, significantly lower WBC counts and absolute neutrophil counts at baseline were seen in nonsmoking patients treated with paclitaxel (P = 0.0001). Pharmacokinetic parameters were similar in smokers and nonsmokers for both taxanes.

Conclusion: Cigarette smoking does not alter the pharmacokinetic determinants of docetaxel and paclitaxel. Smokers treated with docetaxel and paclitaxel have less neutropenia and leukopenia, but further research is warranted to elucidate this potential protective effect. Clin Cancer Res; 18(16); 4425–32. ©2012 AACR.

Introduction

Smoking tobacco is the foremost preventable cause of cancer (1). It has been directly or indirectly linked to more than 10 different tumor types and accounts for 30% of all cancer deaths (2). Despite today’s current insights on the extensive harmful effects of smoking, its prevalence remains high. In 2008, 23.5% of men and 18.3% of women in the United States were smokers (3). Worldwide, there are more than 1.3 billion tobacco smokers and this number is still increasing (4).

Cigarette smoke contains many substances, including polycyclic aromatic hydrocarbons, which are known to induce cytochrome P450 (CYP) metabolic enzymes and some isomers of the uridine diphosphate glucuronosyltransferase (UGT) family which are involved in glucuronic acid conjugation (5). Therefore, smoking might potentially interfere with the pharmacokinetics of several drugs. Currently, it is known that smoking accelerates the metabolism of many different agents (i.e., clozapine, quinine, and propanolol). Especially extra-hepatic localized CYP1A2 and CYP1A1-mediated metabolism is influenced by cigarette smoke (5–6). For example, smokers treated with clozapine have approximately 2.5 times lower serum drug concentrations than nonsmokers, indicating an enhanced clearance (7).

In the recent literature, there are several suggestions that smoking can also modulate the pharmacokinetics of anticancer drugs. Erlotinib, a drug primarily metabolized by CYP3A4 but also by CYP1A2, has a 2.8-fold lower systemic exposure in smokers than in nonsmokers (8). In addition, we have previously shown that smokers treated with irinotecan have an 18% higher clearance than nonsmokers. This produg is primarily metabolized by CYP3A4 and carboxylesterases, and its active metabolite SN-38 is glucuronidated by UGT1A1. The resulting altered balance in the complex metabolism leads to a 40% reduction of systemic exposure to SN-38. The higher relative extent of glucuronidation of SN-38 observed in smokers in this study can be explained by induction of UGT1A1 (9).
Both docetaxel and paclitaxel are antimicrotubular agents extensively metabolized by CYP3A4, whereas CYP2C8 is also involved in the metabolism of paclitaxel (10, 11). These drugs are registered for and used in the treatment of a variety of cancers, such as ovarian, breast, prostate, and non–small cell lung cancer (12). There is a large interindividual variability in the pharmacokinetics of taxanes, their toxicity, and therapeutic response (13, 14). This poses a serious issue for dosing within the narrow therapeutic window of both docetaxel and paclitaxel. Patients with a low docetaxel clearance are at a higher risk of severe adverse events such as febrile neutropenia, and other severe toxicities such as mucositis and skin toxicity (14, 15). A low paclitaxel clearance puts patients primarily at risk for hematologic toxicities (mainly neutropenia) and peripheral neuropathy (16). On the other hand, patients with high clearances are at risk of suboptimal systemic drug levels, potentially leading to a decreased therapeutic effect. Literature data suggest substantial influence by genetic, nutritional, and environmental factors on the pharmacokinetics of paclitaxel (17). At present, many factors contributing to this large interindividual variability remain to be elucidated.

More extensive knowledge of factors influencing the metabolism of docetaxel and paclitaxel may give new prospects in developing individual dosing regimens. Against this background, we conducted a retrospective study to determine the potential effects of smoking behavior on the pharmacokinetics and hematologic toxicities of both docetaxel and paclitaxel in a large cohort of patients with solid tumors.

Patients and Methods

Patients
A total of 566 patients were included in this retrospective analysis. For docetaxel, patients were previously enrolled in 7 different prospective studies, all involving pharmacokinetic analyses, of which one is still ongoing (18–23). For paclitaxel, patients were enrolled in 3 different prospective studies involving pharmacokinetic analyses, of which one is still ongoing (24, 25). The cutoff date for the analysis was August 2011.

The common inclusion criteria for all mentioned studies were (i) a histologically or cytologically confirmed diagnosis of cancer treated with docetaxel or paclitaxel, (ii) aged 18 years or older, (iii) WHO performance score of 0 to 1, and (iv) adequate hematopoietic, hepatic, and renal functions. Patients using drugs known to be potent CYP3A4 inducers or inhibitors were not included in these studies. The medical ethical committee of the Erasmus University Medical Center (Rotterdam, the Netherlands) approved all individual trials, and patients provided written informed consent before participation in a trial.

Treatment
Docetaxel-treated patients generally received a 75 to 100 mg/m² dose, depending on tumor type or combination regimen. Paclitaxel-treated patients generally received either 90 mg/m² weekly or 175 mg/m² every 3 weeks. Patients receiving medication known to influence the pharmacokinetics of docetaxel or paclitaxel were excluded from entry in the study.

Smoking status
Patients were categorized on smoking status according to smoking information from medical files recorded on the day of pharmacokinetic sampling. If smoking status was not entirely clear based on information in the medical records, patients were excluded from the analyses. Patients who had quit smoking within 4 weeks before pharmacokinetic sampling were also excluded, to guarantee a safe “washout period” for potential enzyme induction (or inhibition).

Pharmacodynamic and pharmacokinetic analysis for docetaxel and paclitaxel
Toxicity was graded according to National Cancer Institute–Common Terminology Criteria (NCI-CTC) criteria. Patients were evaluable for toxicity analysis when they received more than one treatment cycle. Occurrence of grade III toxicity was scored for each patient during the whole period of treatment cycles. Baseline white blood cell (WBC) and absolute neutrophil count (ANC) were recorded before start of taxane therapy. Nadir WBC and ANC values were determined as lowest WBC and ANC values during all treatment cycles.

Blood samples for pharmacokinetic analysis of docetaxel or paclitaxel were obtained in up to 3 treatment cycles per patient. Samples were collected in the presence of lithium heparin as anticoagulant. For docetaxel (18–23), 121 and 169 patients, respectively, and for paclitaxel (24, 25), 22 and 254 patients, respectively, were either extensively sampled after the end of infusion, or in a limited sampling strategy, with 4 to 5 samples in up to approximately 24 hours after the end of infusion.

Translational Relevance
The chemotherapeutic agents docetaxel and paclitaxel are known for their small therapeutic window and for their large interindividual variability in metabolism and toxicity profile. Several factors may influence the systemic exposure to these drugs, including genetic factors (i.e., polymorphisms in genes coding for drug transporters) and comedication (i.e., use of strong CYP3A inhibitors). Also, cigarette smoking was identified as a factor influencing the pharmacokinetics and pharmacodynamics of cytotoxic drugs metabolized by CYP3A but was not studied thoroughly for taxanes before. Because of the small therapeutic window, an alteration in drug exposure may easily lead to unexpected toxicities or suboptimal therapeutic effects in individual patients with cancer; therefore, a knowledge of the effects of smoking on taxane therapy is important for the further individualized treatment of docetaxel and paclitaxel treatment.
Docetaxel has been quantitated in plasma by a validated high-performance liquid chromatography (HPLC) method with UV detection (26) or by validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods (19, 27). Paclitaxel has been quantitated by either a validated HPLC method with UV detection (28) or by a validated LC/MS-MS method based on the method described for docetaxel (19).

On the basis of the measured plasma concentrations at different time points and previously developed population pharmacokinetic models for docetaxel (29) and paclitaxel (13) with population Cremophor concentrations (30), individual pharmacokinetic parameters were estimated as empirical Bayes estimates using the nonlinear mixed-effect modeling software NONMEM version VI and 7 (Icon Development Solutions).

Because Cremophor EL, the formulation vehicle of paclitaxel, causes a shift in the blood distribution of paclitaxel and a reduction in the availability of the free circulating fraction of paclitaxel, the total fraction of paclitaxel does not behave in a linear pharmacokinetic way in contrast to the “free” fraction. Therefore, “unbound,” instead of total clearance was used in the analysis (25, 31).

**Statistical analysis**

Data are presented as medians and ranges, unless stated otherwise. To test the difference in continuous variables between smokers and nonsmokers, the Kruskal–Wallis test was used. For the comparison between smoking status and nominal variables, \( \chi^2 \) test was used to calculate a corresponding \( P \) value. To correct for the different tumor types, different dosing, and combination regimens, a logistic regression analysis was used for the pharmacodynamic analysis. A \( P \) value <0.05 was considered to indicate a significant difference. All the statistical analyses were conducted with Stata version 11.1.

**Results**

**Baseline parameters**

In smokers treated with paclitaxel, significantly higher WBC (9.1 vs. 7.1 \( \times 10^9/L; P = 0.0001 \)) and ANC values before start of treatment (6.6 vs. 4.6 \( \times 10^9/L; P = 0.0001 \)) were observed (Table 1). Smokers treated with docetaxel also had higher WBC and ANC values than nonsmokers, but this difference was not significant (Table 2). In both docetaxel- and paclitaxel-treated patients, other basic

**Table 1. Patient characteristics treated with paclitaxel**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Nonsmokers</th>
<th>Smokers</th>
<th>( P^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients(^b)</td>
<td>276 (100)</td>
<td>214 (78)</td>
<td>62 (22)</td>
<td></td>
</tr>
<tr>
<td>Gender(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>140 (51)</td>
<td>112 (80)</td>
<td>28 (20)</td>
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</tr>
<tr>
<td>Female</td>
<td>136 (49)</td>
<td>102 (75)</td>
<td>34 (25)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>60 (18–82)</td>
<td>61 (18–82)</td>
<td>57 (26–73)</td>
<td>0.007</td>
</tr>
<tr>
<td>Tumor type(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal/gastric</td>
<td>118 (43)</td>
<td>91 (77)</td>
<td>27 (23)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>39 (14)</td>
<td>33 (85)</td>
<td>6 (15)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>17 (6)</td>
<td>13 (76)</td>
<td>4 (24)</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>17 (6)</td>
<td>9 (53)</td>
<td>8 (47)</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>17 (6)</td>
<td>16 (94)</td>
<td>1 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>15 (5)</td>
<td>13 (87)</td>
<td>2 (13)</td>
<td></td>
</tr>
<tr>
<td>Head/neck</td>
<td>11 (4)</td>
<td>7 (64)</td>
<td>4 (36)</td>
<td></td>
</tr>
<tr>
<td>(A)CUP</td>
<td>10 (4)</td>
<td>6 (60)</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>6 (2)</td>
<td>4 (67)</td>
<td>2 (33)</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>6 (2)</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>4 (1)</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>3 (1)</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>3 (1)</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Other</td>
<td>10 (5)</td>
<td>9 (10)</td>
<td>1 (10)</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline hematology**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (( \times 10^9/L ))</th>
<th>Nonsmokers (( \times 10^9/L ))</th>
<th>Smokers (( \times 10^9/L ))</th>
<th>( P^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>283 (65–735)</td>
<td>280 (77–735)</td>
<td>289 (65–643)</td>
<td>0.5</td>
</tr>
<tr>
<td>WBC</td>
<td>7.3 (2.3–24)</td>
<td>7.1 (2.3–24)</td>
<td>9.1 (4.8–19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ANC</td>
<td>4.8 (1.2–21)</td>
<td>4.6 (1.2–21)</td>
<td>6.6 (2.1–16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>8.1 (3.4–11)</td>
<td>8.0 (3.4–11)</td>
<td>8.3 (4.1–10)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviation: (A)CUP, adenocarcinoma of unknown primary.

\(^a\)All data are represented as median with range in parentheses, unless stated otherwise.

\(^b\)Number with percentages in parentheses.

\(^c\)Statistically tested with the 2-sided Kruskal–Wallis test.
demographic patient characteristics were quite similar between smokers and nonsmokers, except that in the paclitaxel-treated patients, smokers were younger than nonsmokers (Tables 1 and 2).

Smoking status and docetaxel-related toxicity

In the group of smokers, there was significantly less grade IV neutropenia (ANC < 0.5 \times 10^9/L) in all treatment cycles than in the nonsmoking group (35% vs. 52%; \( P = 0.01 \); Table 3). When corrected in a multivariate analysis for tumor type, different dosing, and combination regimens, this effect remained apparent (OR, 0.48; 95% CI, 0.26–0.89; \( P = 0.02 \)). However, during docetaxel treatment, the incidence of neutropenic fever was similar in both groups (16% vs. 20%; \( P = 0.43 \); Table 3). Smokers treated with docetaxel also had significantly less grade III–IV leukopenia (WBC < 2.0 \times 10^9/L) than nonsmokers (43% vs. 56%; \( P = 0.04 \); Table 3; Fig. 1). When corrected in a multivariate analysis for tumor type, different dosing, and combination regimens, smokers still had fewer grade III–IV leukopenia, although this result was not significant (OR, 0.63; 95% CI, 0.34–1.15; \( P = 0.13 \)).

Smoking status and paclitaxel-related toxicity

There was significantly less WBC grade III–IV toxicity in smokers (12% vs. 25%; \( P = 0.03 \); Table 3; Fig. 1) than in nonsmokers treated with paclitaxel. In a multivariate analysis correcting tumor type, different dosing, and combination regimens, this effect remained significant (OR, 0.31; 95% CI, 0.12–0.82; \( P = 0.02 \)). The WBC nadir was also higher in smokers (3.3 \times 10^9/L) than in nonsmokers (2.7 \times 10^9/L; \( P = 0.02 \)). In patients treated with paclitaxel, there was a trend toward lower incidence of ANC grade III–IV toxicity during all treatment cycles in smokers when compared with nonsmokers (27% vs. 40%; \( P = 0.06 \), Table 3; Fig. 1). The ANC nadir was higher in smokers than in nonsmokers (1.7 vs. 1.3 \times 10^9/L; \( P = 0.04 \); Table 3). However, also during paclitaxel treatment, the incidence of neutropenic fever was similar in both groups (8% vs. 6%; \( P = 0.5 \); Table 3).

Smoking in relation to taxane pharmacokinetics

There was no significant difference in docetaxel and paclitaxel clearance between smokers and nonsmokers. The clearance in patients treated with docetaxel was 39 L/h (range, 3.6–75 L/h) in smokers and 39 L/h (range, 6.1–85 L/h) in nonsmokers. In the patients treated with docetaxel.
paclitaxel, the unbound clearance was 463 L/h in smokers (range, 138–906 L/h) and 450 L/h (range, 157–1,037 L/h) in nonsmokers (Table 4).

Discussion

This is the first study assessing the effects of smoking on the side effects and pharmacokinetics of taxane treatment in a large group of patients with cancer. Cigarette-smoking patients treated with docetaxel or paclitaxel appeared to have less drug-related neutropenia and leukopenia than nonsmokers, which is not explained by altered systemic exposure to these drugs, but could possibly be explained by a significant higher baseline WBC and ANC values in paclitaxel-treated patients and a trend toward higher baseline WBC in docetaxel-treated patients.

The difference in baseline WBC and ANC values between smokers and nonsmokers in paclitaxel-treated patients seen in our study is in line with literature data on healthy humans, where it has extensively been reported that smokers have higher baseline WBC and ANC values (32–34). A possible explanation for this effect is that when alveolar macrophages are stimulated by cigarette smoke constituents, they produce proinflammatory markers such as TNF-α, interleukin (IL)-1, IL-6, IL-8, and several hematopoietic growth factors such as granulocyte macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF; refs. 33, 35). The production of these factors results in increased proliferation and accelerated release of leukocytes from the bone marrow, resulting in a higher leukocyte count (33). Apart from WBCs, other inflammatory markers such as C-reactive protein and fibrinogen are known to be elevated in healthy smokers (36). Because we did not study these parameters, we cannot confirm these findings.

It has been reported that neutropenia and leukopenia experienced during the course of chemotherapy is independently associated with improved survival in different tumor types (37, 38). Therefore, the higher WBC and ANC found in smokers in our study could indicate a weaker biologic effect of taxane treatment. Also, higher pretreatment neutrophil counts have been independently associated with

### Table 3. Effect of smoking behavior on docetaxel and paclitaxel-induced toxicity

<table>
<thead>
<tr>
<th>Parametera</th>
<th>Nc</th>
<th>All patients</th>
<th>Nonsmokers</th>
<th>Smokers</th>
<th>Pd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir (×10^9/L)</td>
<td>213/75</td>
<td>1.8 (0.05–17)</td>
<td>1.73 (0.09–17)</td>
<td>2.5 (0.05–13)</td>
<td>0.5</td>
</tr>
<tr>
<td>Decrease WBC</td>
<td>210/75</td>
<td>76 (0–100)</td>
<td>76 (0–98)</td>
<td>73 (0–100)</td>
<td>0.9</td>
</tr>
<tr>
<td>CTC grade III–IVb</td>
<td>213/75</td>
<td>152 (53)</td>
<td>120 (56)</td>
<td>32 (43)</td>
<td>0.04 e</td>
</tr>
<tr>
<td>ANC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir (×10^9/L)</td>
<td>213/75</td>
<td>0.6 (0.01–15)</td>
<td>0.5 (0.01–15)</td>
<td>0.8 (0.05–12)</td>
<td>0.6</td>
</tr>
<tr>
<td>Decrease ANCf</td>
<td>211/75</td>
<td>91 (0–100)</td>
<td>92 (0–100)</td>
<td>88 (0–100)</td>
<td>0.8</td>
</tr>
<tr>
<td>CTC grade III–IVb</td>
<td>213/75</td>
<td>170 (59)</td>
<td>128 (60)</td>
<td>42 (56)</td>
<td>0.5 a</td>
</tr>
<tr>
<td>CTC grade IVb</td>
<td>213/75</td>
<td>137 (48)</td>
<td>111 (52)</td>
<td>26 (35)</td>
<td>0.01 e</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC grade III–IVb</td>
<td>213/75</td>
<td>55 (19)</td>
<td>43 (20)</td>
<td>12 (16)</td>
<td>0.4 a</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WBC count</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nadir (×10^9/L)</td>
<td>213/60</td>
<td>2.7 (0.05–12)</td>
<td>2.7 (0.05–12)</td>
<td>3.3 (0.08–10)</td>
<td>0.02</td>
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<tr>
<td>Decrease WBCf</td>
<td>213/60</td>
<td>61 (0–100)</td>
<td>61 (0–100)</td>
<td>63 (5.6–98)</td>
<td>0.3</td>
</tr>
<tr>
<td>CTC grade III–IVb</td>
<td>213/60</td>
<td>61 (22)</td>
<td>54 (25)</td>
<td>7 (12)</td>
<td>0.03 e</td>
</tr>
<tr>
<td>ANC</td>
<td></td>
<td></td>
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<tr>
<td>Nadir (×10^9/L)</td>
<td>213/60</td>
<td>1.4 (0.05–9.3)</td>
<td>1.3 (0.05–9.3)</td>
<td>1.7 (0.05–7.5)</td>
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<td>Decrease ANCf</td>
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<td>69 (0–97)</td>
<td>72 (2.6–99)</td>
<td>0.9</td>
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<tr>
<td>CTC grade III–IVb</td>
<td>213/60</td>
<td>101 (37)</td>
<td>85 (40)</td>
<td>16 (27)</td>
<td>0.06 e</td>
</tr>
<tr>
<td>CTC grade IVb</td>
<td>213/60</td>
<td>47 (17)</td>
<td>40 (19)</td>
<td>7 (12)</td>
<td>0.2 e</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CTC grade III–IVb</td>
<td>210/59</td>
<td>18 (7)</td>
<td>13 (6)</td>
<td>5 (8)</td>
<td>0.5 a</td>
</tr>
</tbody>
</table>

aData are represented as median with range in parentheses, unless stated otherwise.

bNumber with percentage in parentheses.

cNumber of patients (nonsmokers/smokers).
dStatistically tested with the 2-sided Kruskal–Wallis test, unless stated otherwise.
eStatistically tested with the χ² test (variable categories vs. smoking status).
fPercentage decrease nadir to baseline.
shorter overall survival and progression-free survival (39, 40), although the underlying mechanism is not clarified yet. These findings highlight the importance of smoking cessation in patients with cancer.

This study was designed to evaluate the effects of smoking on taxane pharmacokinetics. Therefore, patients who quit smoking more than 4 weeks before pharmacokinetic sampling were classified as nonsmokers. However, the higher baseline blood counts in smokers can persist for several years after quitting smoking (32, 41), which might potentially introduce misclassification in smoking status in the toxicity analysis. However, this misclassification is expected to be limited because many patients with cancer continue to smoke after diagnosis (42) or already stopped smoking for other reasons that the discovery of a malignancy. In addition, this misclassification would only lead to an underestimation (instead of overestimation) of the effect of smoking on hematologic counts before start of therapy. Also, nonsmokers who started smoking after pharmacokinetic sampling could potentially bias the results because the time course of de-induction of CYP enzymes is not precisely known. However, we expect this group to be very small or nonexisting at all.

A history of smoking appeared to reduce the incidence of gemcitabine-related severe neutropenia in more than 100 patients with cancer in a study by Kanai and colleagues (43). Only 24% of their smoking patients (including ex-smokers) were found to have grade III–IV neutropenia after gemcitabine treatment, whereas in nonsmokers, this was 56%, suggesting a protective effect (43) in line with our results. Van Erp and colleagues found no protective effect on hematologic toxicities in smokers treated with imatinib (44). Limiting factors of this study are that imatinib infrequently induces neutropenia and that it was a small study including only 15 smokers.

It is known that constituents of cigarette smoke are potent inducers of several drug-metabolizing enzymes. Cigarette smoke can therefore potentially modify the pharmacokinetics and clinical effects of certain drugs. The pharmacokinetics and pharmacodynamics of drugs mainly metabolized by CYP1A are known to be influenced by smoking (5–7). Smoking has also been suggested to induce CYP3A in vitro studies (45, 46) and in a small clinical study on quinine—a known CYP3A substrate (47). Other studies, however, have not confirmed the influence of smoking on CYP3A (48–50). Our group studied the effects of smoking on the adverse effects of irinotecan, which has a complex metabolism, including CYP3A involvement, but also other metabolic routes are involved (9). In agreement with the findings reported here, in that study, a reduced incidence of hematologic toxicity was observed in smokers. These patients had significantly less grade III–IV leukopenia and neutropenia than nonsmokers when treated with single-agent irinotecan. In that study, the lower incidence of hematologic toxicities in smokers was partly explained by significantly lower systemic exposure to irinotecan and its active metabolite SN-38, which might be related to altered CYP3A-mediated metabolism (9). However, influences of

![Figure 1. Incidence of NCI-CTC, version 4, grade III–IV WBC count and ANC during docetaxel (n = 288) and paclitaxel (n = 273) treatment in nonsmokers and smokers. P values are calculated with univariate χ² tests.](image-url)

### Table 4. Effect of smoking behavior on docetaxel and paclitaxel pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parametera</th>
<th>Nb</th>
<th>All patients</th>
<th>Nonsmokers</th>
<th>Smokers</th>
<th>Pc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL, L/h</td>
<td>215/75</td>
<td>39 (3.6–85)</td>
<td>39 (6.1–85)</td>
<td>39 (3.6–75)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paclitaxel (unbound)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL, L/h</td>
<td>214/62</td>
<td>457 (138–1,037)</td>
<td>450 (157–1,037)</td>
<td>463 (138–906)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Abbreviation: CL, clearance, that is, dose divided by area under the curve.

aAll data are represented as median with range in parentheses.
bNumber of patients (nonsmokers/smokers).
cStatistically tested with the 2-sided Kruskal–Wallis test.
other mechanisms, including ATP-binding cassette transporters responsible for the transport of irinotecan and its metabolites, and variation in uridine diphosphate glucuronosyltransferase 1A1 activity which is involved in the glucuronidation of SN-38, cannot be ruled out.

In conclusion, smoking does not alter the pharmacokinetic parameters of docetaxel and paclitaxel. It is therefore unlikely that smoking influences the CYP3A metabolism of drugs. In our study, smokers had less leukopenia and neutropenia than nonsmokers. Further research is warranted to clarify the underlying mechanism of this potential protective effect of smoking on hematologic toxicities in taxane therapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: A.-J. M. de Graan, W.J. Loos, J. Verweij, R.H.J. Mathijssen

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