Toward Prediction of Efficacy of Chemotherapy: A Proof of Concept Study in Lung Cancer Patients Using \([^{11}C]docetaxel\) and Positron Emission Tomography

Astrid A.M. van der Veldt\(^1,2\), Mark Lubberink\(^1,8\), Ron H.J. Mathijssen\(^5\), Walter J. Loos\(^6\), Gerarda J.M. Herder\(^6\), Henri N. Greuter\(^1\), Emile F.I. Comans\(^1\), Hugo B. Rutten\(^7\), Jonas Eriksson\(^1\), Albert D. Windhorst\(^1\), N. Harry Hendriks\(^1,3\), Pieter E. Postmus\(^4\), Egbert F. Smit\(^4\), and Adriaan A. Lammertsma\(^1\)

Abstract

**Purpose:** Pharmacokinetics of docetaxel can be measured in vivo using positron emission tomography (PET) and a microdose of radiolabeled docetaxel (\([^{11}C]docetaxel\)). The objective of this study was to investigate whether a \([^{11}C]docetaxel\) PET microdosing study could predict tumor uptake of therapeutic doses of docetaxel.

**Experimental Design:** Docetaxel-naïve lung cancer patients underwent 2 \([^{11}C]docetaxel\) PET scans; one after bolus injection of \([^{11}C]docetaxel\) and another during combined infusion of \([^{11}C]docetaxel\) and a therapeutic dose of docetaxel (75 mg·m\(^{-2}\)). Compartmental and spectral analyses were used to quantify \([^{11}C]docetaxel\) tumor kinetics. \([^{11}C]docetaxel\) PET measurements were used to estimate the area under the curve (AUC) of docetaxel in tumors. Tumor response was evaluated using computed tomography scans.

**Results:** Net rates of influx (\(K_i\)) of \([^{11}C]docetaxel\) in tumors were comparable during microdosing and therapeutic scans. \([^{11}C]docetaxel\) AUC\(_{tumour}\) during the therapeutic scan could be predicted reliably using an impulse response function derived from the microdosing scan together with the plasma curve of \([^{11}C]docetaxel\) during the therapeutic scan. At 90 minutes, the accumulated amount of docetaxel in tumors was less than 1% of the total infused dose of docetaxel. \([^{11}C]docetaxel\) \(K_i\) derived from the microdosing scan correlated with AUC\(_{tumour}\) of docetaxel (Spearman \(\rho = 0.715; P = 0.004\)) during the therapeutic scan and with tumor response to docetaxel therapy (Spearman \(\rho = -0.800; P = 0.010\)).

**Conclusions:** Microdosing data of \([^{11}C]docetaxel\) PET can be used to predict tumor uptake of docetaxel during chemotherapy. The present study provides a framework for investigating the PET microdosing concept for radiolabeled anticancer drugs in patients. *Clin Cancer Res; 19(15); 4163–73. ©2013 AACR.*

Introduction

Docetaxel belongs to the class of taxanes, which acts by disrupting the microtubular network that is essential for mitosis (1). Initially, the drug was approved as single agent for the treatment of anthracycline refractory advanced breast cancer (2). Thereafter, docetaxel has been approved both as single agent and in combination therapy to treat several advanced malignancies including gastric, head and neck, prostate, and non–small cell lung cancer (3). Nevertheless, docetaxel fails to exert antitumor activity in a substantial number of patients, and it is associated with potentially severe toxicities. Hence, there is a need for a tool to predict efficacy of docetaxel in individual patients.

The response to docetaxel treatment is thought to be directly related to drug concentrations in tumor tissue. As a direct relationship between plasma concentration and efficacy is assumed, it is usual to determine pharmacokinetic profiles in blood (4). Plasma concentrations, however, do not necessarily reflect drug concentrations in tumors (5). In addition, efficacy of docetaxel may strongly depend on maintaining sufficiently high drug concentrations in tumor tissue. In animal studies, sacrifice experiments are commonly carried out to measure drug concentrations in tumors (5). Direct assessment of tumor drug concentrations in patients with cancer, however, is more challenging, as it requires...
accessibility to tumors that are usually deeply seated within the body. In addition, as docetaxel shows nonspecific binding to numerous materials, assessment of docetaxel tumor concentrations by microdialysis is not feasible (6).

Positron emission tomography (PET) is an imaging technique that can be used to monitor drug pharmacokinetics and pharmacodynamics in vivo noninvasively (7). Previously, docetaxel has been labeled with the positron-emitting radionuclide carbon-11 (8, 9), and it has been shown that a dynamic PET scan, following a tracer dose of radiolabeled docetaxel ([11C]docetaxel), provides a quantitative measurement of [11C]docetaxel kinetics in patients with lung cancer (10). In the latter study, tumor kinetics of [11C]docetaxel were found to be highly variable. This, in turn, seemed to be associated with differences in tumor response and, although the number of patients was small, [11C]docetaxel PET studies may hold promise in selecting patients with cancer for docetaxel therapy.

As microdoses of [11C]docetaxel represent less than 1% of the pharmacologic dose, patients are prevented from drug-induced toxicities. However, a potential caveat is the fact that pharmacokinetics of [11C]docetaxel at microdoses (or tracer doses) may be different from those at therapeutic doses. The main aim of this study was to investigate whether an [11C]docetaxel PET microdosing study could predict tumor uptake of unlabeled docetaxel during a therapeutic infusion. To this end, therapeutic tumor uptake of [11C]docetaxel as predicted by spectral analysis of a tracer study was compared with actual measured [11C]docetaxel uptake during an infusion of a therapeutic dose of docetaxel. Furthermore, plasma kinetics of [11C]docetaxel were compared with those of the drug docetaxel during therapeutic infusion. Finally, it was assessed whether simplified analysis of a microdosing study with [11C]docetaxel was in itself sufficient for prediction of tumor uptake of docetaxel during therapeutic infusion.

Materials and Methods

Patient selection

Nine patients with histologically confirmed advanced-stage lung cancer were prospectively enrolled. Inclusion criteria were the following: age ≥ 18 years, a malignant lesion ≥ 1.5 cm in diameter within the chest, scheduled for docetaxel-containing chemotherapy, life expectancy of at least 12 weeks, Eastern Cooperative Oncology Group performance status < 3, hemoglobin ≥ 6.0 mmol/L, and absolute neutrophil count ≥ 1.5 × 10⁹/L. Exclusion criteria were the following: prior treatment with taxanes, concurrent treatment with other anticancer agents or experimental drugs, pregnancy or lactation, metal implants (e.g., pacemakers), and claustrophobia. The study was approved by the Medical Ethics Review Committee of the VU University Medical Center (Amsterdam, the Netherlands). All patients gave written informed consent before study enrollment.

Study design

Patients underwent 2 [11C]docetaxel PET scans on a single day: a tracer alone [11C]docetaxel scan in the morning (further referred to as microdosing scan), and in the afternoon a second tracer [11C]docetaxel scan during an infusion of docetaxel in a therapeutic dose (further referred to as therapeutic scan). For the optimal comparison of microdosing with therapeutic dosing of [11C]docetaxel in a clinical setting, [11C]docetaxel was administered as a bolus injection during the microdosing scan. The therapeutic scan was conducted approximately 4 hours after the microdosing scan. Each [11C]docetaxel scan was combined with a [15O]H₂O scan to measure tumor perfusion. Computed tomography (CT) scans were conducted at baseline and after one or 2 cycles of treatment for evaluation of tumor response to docetaxel therapy.

Synthesis of radiopharmaceuticals

[11C]docetaxel and [15O]H₂O were synthesized according to good manufacturing practice standards as described previously (8, 9, 11). Docetaxel was obtained from Green PlantChem Company Ltd. Docetaxel was chemically modified and used as precursor in the synthesis of [11C]docetaxel. The tracer [11C]docetaxel has an identical molecular structure as the drug docetaxel. [11C]docetaxel was obtained with a decay-corrected radiochemical yield of 10 ± 2% and a radiochemical purity of more than 98%. The identity of [11C]docetaxel was confirmed by comparison of retention times on high-performance liquid chromatography with authentic docetaxel.

Docetaxel therapy

Premedication consisted of oral dexamethasone, 8 mg twice daily, for 3 days starting the day before the PET scans, and 8 mg ondansetron given as an intravenous infusion within 1 hour before docetaxel infusion. Docetaxel was
dissolved in normal saline and was administered as a 1-hour intravenous infusion. \([11C]\)docetaxel was coinfused with the therapeutic dose of docetaxel, simultaneously starting a dynamic PET scan. The nuclear medicine ward and all personnel involved fulfilled the criteria required for administration of chemotherapy according to established safety guidelines.

**Scanning protocol**

Scans were conducted on a PET-CT scanner (Gemini TF-64, Philips Medical Systems; ref. 12), which has an axial field of view of 18 cm, divided into 45 contiguous planes. Patients were asked to fast from midnight before scanning. A light breakfast at 8:00 am and a light lunch at 12:00 pm, and water and tea, were allowed until PET scanning. All patients received 2 venous catheters, one for tracer injection and infusion of therapeutic docetaxel and the other for blood sampling. Patients were positioned supine on the scanner bed, with both tumor and aortic arch located inside the axial field of view of the scanner. Movement during scanning was minimized using elastic body restraining bandages.

Before the microdosing scan with \([11C]\)docetaxel, a \([15O]H_2O\) scan was carried out. This 10 minutes dynamic scan was started simultaneously with an intravenous injection of 370 MBq \([15O]H_2O\) (5 mL at a rate of 0.8 mL sec\(^{-1}\)), followed by a 35 mL saline flush (at a rate of 2 mL sec\(^{-1}\)). Thereafter, a 50 milliampere-seconds (mA) low-dose CT scan was conducted for attenuation correction. At least 20 minutes after administration of \([15O]H_2O\), a 60-minute dynamic scan was started simultaneously with an intravenous injection of \([11C]\)docetaxel (dissolved in a maximum volume of 12 mL saline, at a rate of 0.8 mL sec\(^{-1}\)), followed by 35 mL saline (at a rate of 2 mL sec\(^{-1}\)). During the microdosing scan, the median-injected dose of \([11C]\)docetaxel was 348 MBq (range 230–367 MBq) with a median-specific activity of 10.1 GBq \(\mu\)mol\(^{-1}\) (range 2.0–37.3 GBq \(\mu\)mol\(^{-1}\)). As a result, administration of a typical tracer dose of 370 MBq \([11C]\)docetaxel with a specific activity of approximately 10 GBq \(\mu\)mol\(^{-1}\) contained a total of approximately 30 \(\mu\)g docetaxel. Sequential scans using \([15O]H_2O\) and \([11C]\)docetaxel were possible because of the short half-lives of oxygen-15 and carbon-11, which are 2.0 and 20.3 minutes, respectively. Using the three-dimensional row action maximum likelihood reconstruction algorithm, \([15O]H_2O\) and \([11C]\)docetaxel scans were reconstructed into 26 (1 \(\times\) 10, 8 \(\times\) 5, 4 \(\times\) 10, 2 \(\times\) 15, 3 \(\times\) 20, 2 \(\times\) 30, and 6 \(\times\) 60 s) and 36 (1 \(\times\) 10, 8 \(\times\) 5, 4 \(\times\) 10, 2 \(\times\) 15, 3 \(\times\) 20, 2 \(\times\) 30, 6 \(\times\) 60, 4 \(\times\) 150, 4 \(\times\) 300, and 2 \(\times\) 600 s) frames, respectively. All data were normalized, and all appropriate corrections were applied for dead time, decay, randoms, scatter, and attenuation.

During the therapeutic study, the \([15O]H_2O\) scan was conducted after the therapeutic scan with \([11C]\)docetaxel. First, a 50 mAs low-dose CT scan was conducted. Then, \([11C]\)docetaxel and docetaxel therapy were administered as an infusion through the same venous catheter. To this end, an injection tube with \([11C]\)docetaxel (median dose, 359 MBq; range, 196–531 MBq; dissolved in a volume of 50 mL saline) and a plastic flexi-bag containing a therapeutic dose of docetaxel (dissolved in a volume of 520–540 mL) were connected with flexible infusion lines to the same venous catheter. To prevent scatter from \([11C]\)docetaxel in the injection tube, a lead castle was built around the infusion pump that contained the tube. Two infusion pumps were used to control the speed of the infusions of \([11C]\)docetaxel and therapeutic docetaxel separately. The administration of \([11C]\)docetaxel and therapeutic docetaxel was scheduled in such a way that \([11C]\)docetaxel and docetaxel entered the venous catheter at identical time points. Simultaneously, a 90-minute dynamic scan was started. As patients received their first docetaxel infusion, the infusion was given at a slower rate for the first 15 minutes (\([11C]\)docetaxel at a rate of \(0.007\) mL sec\(^{-1}\) and docetaxel therapy at a rate of \(0.075\) mL sec\(^{-1}\)). Thereafter, if patients did not experience any side effects, infusion rates of \([11C]\)docetaxel and docetaxel therapy were increased to \(0.014\) mL sec\(^{-1}\) and \(0.150\) mL sec\(^{-1}\), respectively. At the time when the infusion of therapeutic docetaxel had been completed, \([11C]\)docetaxel infusion was discontinued, and saline (100 mL at a rate of 600 mL/h\(^{-1}\)) was infused subsequently. Thereafter, the remaining \([11C]\)docetaxel in the tube was measured to calculate the actual injected dose of \([11C]\)docetaxel. Immediately after the 90-minute \([11C]\)docetaxel scan, a 50 mAs low-dose CT scan was conducted. This was followed by a 10.5-minute dynamic \([15O]H_2O\) scan. After thirty seconds into this scan, 370 MBq \([15O]H_2O\) (5 mL at a rate of \(0.8\) mL sec\(^{-1}\)) was injected intravenously, followed by a 35 mL saline flush (at a rate of 2 mL sec\(^{-1}\)). \([11C]\)docetaxel and \([15O]H_2O\) scans from the therapeutic scan were reconstructed into 25 (1 \(\times\) 600, 10 \(\times\) 60, and 14 \(\times\) 300 sec) and 27 (1 \(\times\) 10, 8 \(\times\) 5, 4 \(\times\) 10, 2 \(\times\) 15, 3 \(\times\) 20, 2 \(\times\) 30, 6 \(\times\) 60 sec) frames, respectively.

**Blood sampling**

After intravenous injection of \([11C]\)docetaxel, sequential 10 mL venous samples were collected in glass tubes containing lithium heparin. During microdosing and therapeutic scans, these samples were taken at 2.5, 5, 10, 15, 20, 30, 40, and 60 minutes postinjection and at 10, 20, 30, 40, 50, 60, 70, and 80 minutes after start of infusion, respectively. Before each sample, 3 to 5 mL blood was discarded, and after each sample the line was flushed with 2 mL saline. Blood samples were analyzed for whole blood and plasma concentrations of \([11C]\)docetaxel. In addition, blood samples obtained during the therapeutic scan were analyzed for radiolabeled metabolites of \([11C]\)docetaxel (10). Samples obtained from the microdosing scan were not analyzed for radiolabeled metabolites, as these had not been detected in a previous microdosing study (10). Whole blood (0.5 mL) was weighted in duplicate and 0.05 mL 10% Triton X-100 solution was added. After centrifuging the remaining whole blood (5 minutes; room temperature; 4,000 rpm), plasma was harvested, and 0.5 mL plasma was weighted in duplicate, again adding 0.05 mL 10% Triton X-100 solution. A well-counter, cross calibrated against the PET scanner, was used to determine activity concentrations.
In addition, plasma samples collected during the therapeutic scan were stored at −80°C until further analysis. Total plasma concentrations of docetaxel were determined using liquid chromatography coupled to tandem mass-spectrometric detection as previously described (13). Trapezoidal integration was used to calculate the area under the plasma curve (AUC\text{Plasma}) of docetaxel.

To verify that plasma kinetics of [11C]docetaxel and docetaxel were identical during the therapeutic scan, radioactivity concentrations of [11C]docetaxel in plasma were divided by the specific activity of infused [15C]docetaxel during the therapeutic scan and compared with measured total docetaxel plasma concentrations.

**Input functions**

The ascending aorta in the [15O]H2O and [11C]docetaxel images was used for generating noninvasive image-derived input functions, as validated previously (10, 14). Volumes of interest (VOI) of 1 cm diameter were drawn over the ascending aorta in approximately 10 consecutive image planes of the frame in which the first pass of the bolus was best visualized. Projection of these VOIs onto all image frames yielded the arterial time–activity curve [TAC (CA(t))]. For the [15O]H2O images, a similar approach was used for the pulmonary artery in approximately 5 consecutive planes, thereby providing a TAC for the pulmonary circulation CA(t); ref. 14). Furthermore, the image-derived input function of [11C]docetaxel was obtained by multiplying CA(t) with a sigmoid function describing the measured [15C]docetaxel concentrations) for any plasma input function by convolution with that plasma input function. For the [11C]docetaxel microdosing scans, tumor IRFs were determined using spectral analysis with 50 basic functions and clearance rate constants ranging from 0 to 1 minutes⁻¹. Next, this IRF was convolved with the [11C]docetaxel plasma input function of the therapeutic scan, resulting in a prediction of tumor TACs during therapy (16). Bootstrap analysis was conducted to estimate the confidence intervals of the IRF and the predicted tumor TAC during the therapeutic scan (17). Areas under the predicted and measured tumor TACs (AUCTumor) for [11C]docetaxel during infusion of the therapeutic dose were compared.

**Tumor uptake of docetaxel**

To further verify whether an [11C]docetaxel Kᵢ from the microdosing scan predicts kinetics of docetaxel during therapy, the amount of docetaxel in tumor tissue was calculated according to 2 different methods. First, the accumulated amount of docetaxel in tumors was calculated by multiplication of [11C]docetaxel Kᵢ obtained from the microdosing scan with the AUC\text{Plasma} of docetaxel during the therapeutic scan. Alternatively, the concentration of docetaxel at the last time point of the therapeutic scan was calculated by dividing the radioactivity concentration at 90 minutes by the mean specific activity of [11C]docetaxel in plasma. Second, the AUC\text{Tumor} of total docetaxel during the therapeutic scan was calculated by dividing the measured AUC\text{Tumor} of [11C]docetaxel during the same scan by the mean specific activity of [11C]docetaxel in plasma. The schematic diagram in Supplementary Fig. S1 illustrates the analyses that were carried out to calculate the amount of docetaxel in tumor tissue. Finally, the absolute amount of docetaxel in tumor was determined by multiplication with the corresponding tumor volume.

**Tumor response to docetaxel treatment**

Response to docetaxel treatment was determined on sequential CT scans. To this end, one-dimensional changes in tumor size (18) were assessed by measuring the longest
diameter of each tumor that could be defined in the field of view of the dynamic PET scan.

Statistical analysis

Statistical analysis was conducted using SPSS software (SPSS for Windows 16.0, SPSS, Inc.). The Wilcoxon signed rank test was used to compare variables obtained from microdosing with therapeutic scans. The Spearman correlation coefficient was used to explore correlations. A 2-tailed probability value of $P < 0.05$ was considered significant.

Results

Patients and PET scanning

At the time of the study, all patients were diagnosed with histologically proven non–small cell lung cancer. Retrospectively, however, one patient was diagnosed with thymic carcinoma after surgical resection of the primary tumor. In 6 patients (4 males and 2 females; median age 68 years; range 46–74 years), both $[11C]$docetaxel scans were evaluable for analysis. In the remaining patients, the second $[11C]$docetaxel scan could not be conducted because of technical difficulties. All patients underwent a $[15O]$H2O scan as part of the microdosing scan, whereas 4 out of 6 patients underwent an additional $[15O]$H2O scan as part of the therapeutic scan. The therapeutic dose of docetaxel was administered at 75 mg $m^{-2}$ with a median dose of 150 mg (range 110–170 mg). Patients did not experience any acute side effect during infusion of therapeutic docetaxel. The median time of docetaxel infusion was 66 minutes (range 62–74 min). None of the patients used comedication consisting of inhibitors or substrates of the efflux transporter ABCB1. Following the $[11C]$docetaxel PET study, 3 patients were subsequently treated with a platinum compound.

Plasma kinetics of $[11C]$docetaxel correlate with docetaxel kinetics during therapeutic infusion

Infusion of $[11C]$docetaxel during the therapeutic scan resulted in different arterial plasma curves of $[11C]$docetaxel than those obtained during the microdosing scan (Fig. 1). Radiolabeled metabolites of $[11C]$docetaxel could not be detected during the therapeutic scan, confirming previous results for tracer $[11C]$docetaxel studies (10). During the therapeutic scan, plasma curves of $[11C]$docetaxel were similar to those of docetaxel (Figs. 1B and 2A), which were similar to those of historical controls (Fig. 2A; ref. 19). Median AUC$_{Plasma}$ of docetaxel was 2.23 $\mu$g mL$^{-1}$ h (range 1.75–3.42 $\mu$g mL$^{-1}$ h). When plasma concentrations of docetaxel during therapeutic infusion were calculated on the basis of measured radioactivity concentrations in plasma and infused doses of $[11C]$docetaxel and docetaxel, there was a high correlation between measured and calculated plasma concentrations of docetaxel (Spearman $\rho = 0.850$; $P < 0.001$; Fig. 2B).

$K_i$ values of $[11C]$docetaxel in tumors are comparable during microdosing and therapeutic scan

Fourteen tumors with a median size of 3 cm$^3$ (range 1–334 cm$^3$) could be defined on the low-dose CT scans. Figure 3 shows TACs of $[11C]$docetaxel in tumors during microdosing and therapeutic scans. During the time frame of the therapeutic scan, therapeutic infusion of docetaxel resulted in progressive accumulation of $[11C]$docetaxel in tumor tissue. During microdosing and therapeutic scans, median $K_i$ values of $[11C]$docetaxel in tumors were $0.0078$ mL cm$^{-3}$ minute$^{-1}$ (range 0.0023–0.0228 mL cm$^{-3}$ minute$^{-1}$) and $0.0077$ mL cm$^{-3}$ minute$^{-1}$ (range 0.0023–0.0152 mL cm$^{-3}$ minute$^{-1}$), respectively. These $K_i$ values were highly variable between and within patients. There was a trend toward a correlation between $K_i$ values of $[11C]$docetaxel obtained from microdosing and therapeutic scans (Spearman $\rho = 0.473$; $P = 0.088$). Although therapeutic infusion changed $K_i$ of $[11C]$docetaxel in some tumors, overall there was no significant difference (Wilcoxon signed rank test, $P = 0.507$). Both during microdosing and therapeutic scans, $K_i$ of $[11C]$docetaxel was related to tumor perfusion (Spearman $\rho = 0.662$ and 0.775; $P = 0.010$ and 0.007, respectively). After therapeutic infusion, tumor perfusion did not change (Wilcoxon signed rank test, $P = 0.131$).

![Figure 1. Whole blood and plasma concentrations of $[11C]$docetaxel in the ascending aorta as function of time for (A) a microdosing scan (tracer dose only) and (B) a therapeutic scan (coinfusion with a pharmacologic dose of docetaxel). In B, the infusion was discontinued at 62 minutes.](www.aacjournals.org)
$[^{11}C]$docetaxel microdosing predicts AUC$_{\text{Tumor}}$ of $[^{11}C]$docetaxel during therapeutic infusion

As $K_i$ only represents the net rate of influx of $[^{11}C]$docetaxel in tumor tissue, the AUC$_{\text{Tumor}}$ of $[^{11}C]$docetaxel was used as a measure of $[^{11}C]$docetaxel exposure of tumors during the therapeutic scan. During the 90 minutes therapeutic scan, the median AUC$_{\text{Tumor}}$ of $[^{11}C]$docetaxel was measured to be 285 kBq min mL$^{-1}$ (range 110–634 kBq min mL$^{-1}$). In addition, the AUC$_{\text{Tumor}}$ of $[^{11}C]$docetaxel during the therapeutic scan was predicted from the IRF (Fig. 4A), obtained using spectral analysis of the microdosing scan, together with the plasma $[^{11}C]$docetaxel curve during the therapeutic scan. Figure 4B shows a representative example of such a predicted AUC$_{\text{Tumor}}$ of $[^{11}C]$docetaxel during a therapeutic scan. There was a high correlation between measured and predicted AUC$_{\text{Tumor}}$ of $[^{11}C]$docetaxel (Spearman $r = 0.807$; $P < 0.001$).

Accumulated amount of docetaxel in tumor tissue can be determined from the microdosing scan

As accumulation of docetaxel in tissue depends on its plasma concentrations, the accumulated amount of docetaxel in tumors was calculated by multiplying the AUC$_{\text{Plasma}}$ of docetaxel during the therapeutic scan. At 90 minutes after the start of docetaxel infusion, the median accumulated amount of docetaxel was 1.56 mg cm$^{-3}$ (range 0.24–2.90 mg cm$^{-3}$), which showed a trend with the concentration of docetaxel at the last time point of the therapeutic scan (Spearman $r = 0.516$; $P = 0.059$). When the accumulated docetaxel amount was multiplied with the corresponding tumor volume, the median accumulated amount of docetaxel in tumors was 5.58 mg (range 1.85–542.66 mg), corresponding with $0.0036\%$ (range $0.0011\%–0.4933\%$) of the total infused dose of docetaxel.

Figure 2. Plasma concentrations of docetaxel. A, plasma concentrations of docetaxel during infusion of a therapeutic dose as function of time in the present study (filled circles) and in historical controls (open squares). In the present study, the infusion rate of docetaxel was comparable with that in historical controls (19). B, measured versus calculated plasma concentrations of docetaxel. Calculated concentrations were based on measured $[^{11}C]$docetaxel plasma concentrations and infused doses of $[^{11}C]$docetaxel and docetaxel. To that end, radioactivity concentrations of $[^{11}C]$docetaxel in plasma were divided by the specific activity of infused $[^{11}C]$docetaxel during the therapeutic scan. The solid line is a regression line. $\rho$, Spearman correlation coefficient; $P$, $P$ value.

Figure 3. Tumor concentrations of $[^{11}C]$docetaxel as function of time for (A) a microdosing scan (tracer dose only) and (B) a therapeutic scan (coinfusion with a pharmacologic dose of docetaxel). The fit in A is the best fit for a 2-tissue irreversible compartment model. Filled circles, measured radioactivity concentrations in tumor tissue.


$[^{11}C]$docetaxel $K_i$ from the microdosing scan correlates with AUC$_{Tumor}$ of docetaxel during the therapeutic scan

On the basis of the measured AUC$_{Tumor}$ of $[^{11}C]$docetaxel during the therapeutic scan, the AUC$_{Tumor}$ of docetaxel could also be calculated. At 90 minutes of the therapeutic scan, the median AUC$_{Tumor}$ of docetaxel was 1.69 $\mu$g mL$^{-1}$ hour (range 0.63–2.80 $\mu$g mL$^{-1}$ hour), which correlated with the accumulated amount of docetaxel at 90 minutes (Spearman $\rho = 0.675; P = < 0.001$). In addition, AUC$_{Tumor}$ of docetaxel showed a good correlation with the $[^{11}C]$docetaxel $K_i$ value and tumor perfusion from the microdosing scan (Spearman $\rho = 0.715$ and 0.653; $P = 0.004$ and 0.011, respectively).

Tumor uptake of $[^{11}C]$docetaxel is associated with tumor response to docetaxel therapy

Nine out of 14 tumors could be evaluated for tumor response. The other five tumors could not be evaluated because of clinical deterioration of one patient, precluding further CT assessment. At evaluation, the median change in the longest tumor diameter was 7% (range −6%–100%; see also Supplementary Table S1). In this limited number of tumors, there was a negative correlation between the accumulated amount of docetaxel in tumors (obtained by multiplication of $K_i$ from the microdosing scan and AUC$_{Plasma}$ docetaxel; units in $\mu$g cm$^{-3}$) and the percentage change in longest tumor diameter (Spearman $\rho = −0.717; P = 0.030$). Similarly, $[^{11}C]$docetaxel $K_i$ and perfusion obtained from the microdosing scan showed a negative correlation with the change in the longest diameter (Spearman $\rho = −0.800$ and −0.650; $P = 0.010$ and 0.058, respectively). For the purpose of illustration, Figs. 5 and 6 show examples of sequential CT images in a patient with relatively high $[^{11}C]$docetaxel uptake and in another patient with relatively low $[^{11}C]$docetaxel uptake.

Discussion

The concept of PET microdosing may be used to obtain important information on the distribution and kinetics of drugs in humans (20, 21). In particular, PET studies using tracer doses (so called microdoses) of anticancer drugs may speed up drug development and could be an essential step in personalized treatment planning in oncology. On the basis of this concept, numerous anticancer drugs have been radiolabeled (22). Nevertheless, PET microdosing has not been validated appropriately in a clinical setting. The present study evaluated the principle of PET microdosing for $[^{11}C]$docetaxel in patients with lung cancer. Although microdosing and therapeutic scans showed different TACs of $[^{11}C]$docetaxel in both plasma and tumor tissue, tumor uptake of therapeutic docetaxel could be predicted on the basis of the $[^{11}C]$docetaxel $K_i$ derived from the microdosing scan. In addition, preliminary data showed a relationship between $[^{11}C]$docetaxel $K_i$ and tumor response to docetaxel therapy.

In line with previous $[^{11}C]$docetaxel tracer studies (10), no radiolabeled metabolites of $[^{11}C]$docetaxel were detected during therapeutic infusion. Following a 1-hour infusion of 100 mg m$^{-2}$ docetaxel, metabolites have been detected previously in about one third of patients at 5 to 30 minutes (23). In the liver, docetaxel usually is metabolized by the cytochrome P450 enzyme CYP3A4 into 4 major metabolites (24), which are less cytotoxic than the parent compound (25). This extensive liver metabolism is reflected by high hepatic uptake of the tracer $[^{11}C]$docetaxel (26, 27). The absence of radiolabeled metabolites of $[^{11}C]$docetaxel indicates that no detectable radiolabeled metabolites of $[^{11}C]$docetaxel enter plasma, at least not during the time course of a PET study. Consequently, radioactivity measured in tumors can be attributed solely to the presence of $[^{11}C]$docetaxel.

As expected, plasma TACs of $[^{11}C]$docetaxel were quite different for microdosing and therapeutic scans due to the...
differences in administration protocols, that is bolus injection versus slow infusion. In line with these differences, tumor TACs were also different between microdosing and therapeutic studies. Although plasma concentrations of \([11C]docetaxel\) decreased rapidly after discontinuation of the infusion, tumor TACs still showed accumulation of \([11C]docetaxel\). Retention of \([11C]docetaxel\) in tumor tissue at later times could not be confirmed, as the total duration of a PET scan is limited by the short half-life of carbon-11 (20.3 min). Nevertheless, it is reasonable to assume that achieved tumor concentrations of docetaxel persist at later time points, as retention of docetaxel in tumors has been measured for 24 hours in a mouse study (5).

Despite differences in the administration schedule, \(K_i\) values of \([11C]docetaxel\) were similar during microdosing and therapeutic studies. During a therapeutic infusion, this \([11C]docetaxel\) \(K_i\) is a direct measure of the rate of influx of docetaxel in tumor tissue. Using \([11C]docetaxel\) \(K_i\), however, the availability of docetaxel in plasma is not taken into account. Therefore, as a measure of overall docetaxel uptake in tumor tissue, the AUC\(_{Tumor}\) of \([11C]docetaxel\) was determined during therapeutic infusion of docetaxel. In addition, it was possible to predict this AUC\(_{Tumor}\) of \([11C]docetaxel\) using the IRF derived from the correspond-
investigate how chemotherapy can be delivered more effectively to tumors. In this respect, drug-loaded microbubbles are promising for enhancement of drug delivery to tumor tissue, as these microbubbles can be applied for localized delivery in target tissue by ultrasound triggering (28). In addition, the direct effects of other (anticancer) drugs on metabolism as well as drug delivery to tumors need to be investigated, as other drugs may affect metabolism and drug delivery to tumors. In a recent study, we have shown that the antiangiogenic drug, bevacizumab, induces a rapid and significant reduction in delivery of $^{[11C]}$docetaxel to tumors in patients with non–small cell lung cancer (29).

Furthermore, results of the present study and previous studies (10, 29) indicate that perfusion is an important determinant for docetaxel delivery to tumors. Although docetaxel has antiangiogenic effects in tumors (30), the present study did not reveal immediate effects of docetaxel infusion on tumor perfusion. More importantly, the present findings suggest that tumor perfusion is a predictor of docetaxel exposure and consequently tumor response to docetaxel therapy. As tumor perfusion measurements using $^{[15O]}$H$_2$O PET are relatively simple (14), it may be worthwhile to conduct further studies on the predictive value of tumor perfusion on response to chemotherapy (31).

The results of this study show that the kinetics of $^{[11C]}$docetaxel are linear during the first hour of a therapeutic infusion. However, this finding will not be generic and cannot be extrapolated to other anticancer drugs. Therefore, the PET microdosing concept needs to be validated for the other radiolabeled anticancer drugs as well (22). In addition, the measured drug concentrations in tumor tissue may be partly determined by nonspecific...
binding. PET, however, cannot reveal the drug concentration that is actually available for binding to the therapeutic target. Alternatively, future PET studies should examine the tumor heterogeneity within the uptake kinetics of a radiolabeled drug. In this regard, it may be worthwhile to develop software to analyze the association between regional perfusion and regional drug uptake within tumors.

In conclusion, the current study validated the PET microdosing concept for $^{11}$C-docetaxel in patients with lung cancer. Microdosing data of $^{11}$C-docetaxel could be used to reliably predict tumor uptake of docetaxel during chemotherapy, which was also associated with tumor response to docetaxel therapy. The present study provides a framework for investigating the PET microdosing concept for other radiolabeled anticancer drugs in patients.

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

Authors' Contributions
Conception and design: A.A. van der Veldt, M. Lubberink, R.H.J. Mathijssen, R.H.J. Mathijssen, P.E. Postmus
Development of methodology: A.A. van der Veldt, M. Lubberink, R.H.J. Mathijssen, P.E. Postmus
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.A. van der Veldt, R.H.J. Mathijssen, G.J. Herder, H.N. Greuter, H. Rutten, J. Eriksson, A.D. Windhorst, P.E. Postmus, E.F. Smit
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.A. van der Veldt, M. Lubberink, R.H.J. Mathijssen, W. Loos, E.F. Comans, E.F. Smit, A.A. Lammertsma
Preparation of figures and tables: R.H.J. Mathijssen
Collection and assembly of data: R.H.J. Mathijssen

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Writing, review, and/or revision of the manuscript: A.A. van der Veldt, M. Lubberink, R.H.J. Mathijssen, W. Loos, J. Eriksson, A.D. Windhorst, H. Hendrikse, P.E. Postmus, E.F. Smit, A.A. Lammertsma
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.A. van der Veldt, M. Lubberink, H. N. Greuter, J. Eriksson
Study supervision: A.A. van der Veldt, M. Lubberink, A.A. Lammertsma

Acknowledgments
The authors thank all patients who participated in this study. Suzette van Balen, Amina Elouahmani, Judith van Is, Robin Hemminga, Femke Jongma, Nghi Pham, Nassarah Sai, and Jeroen Wilhelmus for scanning the patients, Natasja Kok, Ilona Pompstra, Aite van Wijk, Sabri Duzenli, Martijn Groenendijk, Esther Nossett, Daniela Oprea-Lager, Atila Pasic, Suzy Samis, Annelies van Schie, and Serge van Wollerem for help with logistical planning and patient care, Dennis Boersma, Marc Huismans, Arthur van Lingen, Henk Plag, and Maqsood Yaquib for technical assistance, Ineke van der Jagt for help with safety procedures required for administration of chemotherapy, Ilse Rutten-Vermelsfoort for help with recruitment of patients, Marien Mooijer, Anneloes Rijnders, Dennis Laan, and Rob Klok for production of $^{11}$C-docetaxel, and Marissa Rongen, Robert Schuit, and Kevin Takkenkamp for production of $^{15}$O$^2$H$^2$O and analysis of blood samples.

Grant Support
This work was financially supported by Cancer Center Amsterdam. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received December 9, 2012; revised March 27, 2013; accepted April 8, 2013; published OnlineFirst April 25, 2013.


Toward Prediction of Efficacy of Chemotherapy: A Proof of Concept Study in Lung Cancer Patients Using $[^{11}\text{C}]$docetaxel and Positron Emission Tomography

Astrid A.M. van der Veldt, Mark Lubberink, Ron H.J. Mathijssen, et al.