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ORIGINAL ARTICLE

Docetaxel pharmacokinetics and its correlation with two in vivo probes for cytochrome P450 enzymes: the C^{14}-erythromycin breath test and the antipyrine clearance test

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Abstract
Background Docetaxel has marked inter-patient PK variability, and metabolic phenotypic probes may enable individualised dosing. This is the first report directly comparing the erythromycin breath test (EBT) (a CYP3A4 probe) with the antipyrine clearance test (ACT), (a general CYP-P450/predominant CYP3A4 probe) for the correlation with docetaxel PK and toxicity.

Methods Patients pretherapy underwent: (A) EBT: IV C^{14}[N-methyl]-erythromycin was administered and breath samples analysed for $^{14}CO_2$, derived parameters included (1) $^{14}CO_2$ flux at 10-min (CO_2f_{10}), (2) 20-min (CO_2f_{20}), (3) terminal rate constant k_{CO2} and (4) $AUC_{CO2,(0-\infty)}$ and $AUC_{CO2,(0-60)}$. (B) ACL test: patients were given oral antipyrine 10 mg/kg, blood samples were taken for PK, and the clearance (CL_{Ant}) was derived. Docetaxel was then given at 75 mg/m^2/3-weekly or 35 mg/m^2/weekly. Samples taken for docetaxel PK in first course on day 1 and PK parameters included clearance (CL_{Doc}).
Results Twenty patients accrued, docetaxel: 3-weekly/weekly = 13:7. EBT parameters ($N = 19$) (mean, [CV%]): CO_2f_{10} (%/min) 0.051 (106), CO_2f_{20} 0.052 (82), k_{CO2} (min^{-1}) 0.007 (22), $AUC_{CO2,(0-\infty)}$ 7.9 (85), $AUC_{CO2,(0-60)}$ 2.64 (81). CL_{Ant} ($N = 19$) (ml/min); 35.8 (37). Docetaxel PK parameters ($N = 19$): CL_{Doc} (l/h) = 57.2 (36), $t_{Doc1/2}$ (h) = 12.7 (33). No correlations were observed between the docetaxel PK and EBT parameters. For docetaxel weekly patients, a significant linear relationship was observed between CL_{Doc} and CL_{Ant} ($P = 0.007$, $R^2 = 79.47\%$).
Conclusions The utility of EBT for the prediction of docetaxel PK was not confirmed in this study. The antipyrine clearance test may be superior in this regard for docetaxel, but regimen dependent and hence warrants further evaluation.

Keywords Docetaxel · In vivo probes · Erythromycin breath test · Antipyrine

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Introduction

The clinical use of cytotoxics is characterised by a narrow therapeutic index, due to the marked inter-patient

variability in their drug handling and pharmacodynamics, with obvious consequences in terms of toxicity and possibly response. The source of variability is related to the patient's physiological state, genotype, the effects of the disease/treatment and dosing practices. It has been the usual practice to dose cytotoxics using body surface area (BSA), in an attempt to reduce this inter-patient PK/PD variability. Unfortunately, BSA-based dosing does not achieve this for the vast majority of cytotoxics [17].

Docetaxel, a taxane, is one such drug, with a large inter-patient variability in clearance (CL) ranging from 30 to 50% associated with variability in toxicity [5, 20, 45]. Pharmacokinetic (PK)-guided (area under the plasma concentration versus time curve [AUC] targeted), individualised docetaxel dosing has been evaluated using a limited sampling strategy in combination with a validated population PK model, Bayesian analysis, and a predefined target AUC. The inter-individual variability, standard deviation of ln(AUC), was decreased by 35% ($N = 15$) after 1 PK-guided course, with a resultant reduction in the variability of myelosuppression [9].

Alternative approaches for dosing have also included phenotyping relevant metabolic enzymes, through the use of probes metabolised by the same or similar pathways as per the cytotoxic. Docetaxel is a pure CYP3A4 substrate [26], and has undergone extensive evaluation by such probes [19, 45], including the C^{14}[N-methyl]-erythromycin breath test (EBT) [34]. CYP3A4 selectively N-demethylates intravenous C^{14}[N-methyl]-erythromycin with the cleaved carbon being expired as $^{14}CO_2$. Measurement of the exhaled $^{14}CO_2$ provides an indirect quantification of hepatic CYP3A4 activity [24, 42]. The EBT though has been inconsistently correlated with docetaxel clearance (CL_{Doc}) [3, 20, 21, 35, 38], as it may actually reflect hepatic ABC-B1 function rather than CYP3A activity [23]. The EBT methodology also presents logistic issues in terms of its applicability in the general clinical setting [9].

Antipyrine is metabolised by several CYP-P450 enzymes (CYP1A2, CYP2B6, CYP2C8 and CYP3A4) and is widely used as a measure of overall hepatic oxidative capacity [8, 13, 25, 39]. Ketoconazole, via CYP3A4 inhibition, reduces antipyrine metabolite formation by up to 80% in human liver microsomal studies. This implies that antipyrine metabolism is predominantly by CYP3A4 [8]. Antipyrine has also been used as a probe for the evaluation of the PK of other cytotoxics [29]. The ACT may present some advantages relative to the EBT, as antipyrine is not an ABC-B1 substrate, as well as being a simple and relatively inexpensive to perform: it requires only 2 blood samples following an oral dose, and blood levels are then measured by routine HPLC analysis. The ACT has been recently correlated with the risk of neutropenia in patients receiving docetaxel and cisplatin [27]. The antipyrine CL test (ACT) may thus be a more practical predictor of $CL_{Doc.}$

The aim of this exploratory trial was thus to identify the relationship between docetaxel PK and toxicity with (1) the EBT parameter(s) and (2) antipyrine CL.

Patients and methods

Patients

Eligible patients met the following criteria: (1) suitable for treatment with docetaxel; (2) ECOG performance status (PS) 0–2; (3) measurable/evaluable disease; (4) no previous chemotherapy within 3 weeks of trial entry; (5) normal organ function such as (i) hepatic: serum (Se) bilirubin $\leq 1.0 \times$ UNL, AST/ALT $\leq 1.5 \times$ UNL and ALP $\leq 2.5 \times$ UNL, (ii) renal: serum creatinine $\leq 160\mu$mol/l, (iii) bone marrow: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l; and (6) written informed consent.

Patients were excluded for the following: (1) any uncontrolled infection, (2) history of other cancer (except non-melanoma skin cancer or cervical carcinoma in situ) unless in complete remission for $\geq$5 years, (3) uncontrolled CNS metastases, and (4) pregnant or lactating women.

Baseline evaluation

At baseline patients underwent clinical evaluation, documentation of concurrent medications, and blood samples taken for haematology and biochemistry (serum urea and electrolytes, hepatic biochemistries) of hepatic synthetic parameters (prothrombin time, INR), acute-phase reactants (C-reactive protein [CRP]) and tumour staging by CT scan, within 3 weeks of trial entry.

In vivo probes

The erythromycin breath test (EMBT):

The breath test was performed within 3 days prior to the first docetaxel dose in the Department of Nuclear Medicine, St. Vincent's Hospital [33].

(i) Sample preparations:

Patient Sample: The C^{14}-erythromycin was prepared for individual patient use by reconstituting $\sim$148 kBq (4 μCi) of C^{14}[N-methyl]-erythromycin (New England Nuclear Boston, MA) in 2 ml of 5% dextrose in water. Prior to administration, the solution was diluted to a total volume of 12 ml in normal saline: 10 ml was drawn up to be administered and 2 ml was set aside for the preparation of the reference solution.

Preparation of Reference: A reference solution was prepared by diluting 1.0 ml from the residual patient solution in 99 ml of 100% ethanol into a 100-ml volumetric flask.

Breath capture: Patients were rested for 15 min prior to the test and during this time, practiced the required breathing procedure. On the final practice breath, they exhaled into a vial containing the CO_2 trapping solution: this sample was used as the counting background. The test commenced when the patients received an IV bolus of C^{14}[N-methyl]-erythromycin at time $T = 0$ min. Patients then provided breath samples at $T = 5$, 10, 20, 30, 40, 60, 90 and 120 min.

Patients exhaled through a plastic straw into 4 ml of the capture solution as a single breath. The breath capture solution consisted of 0.5 M hyamine solution (achieved by mixing 1 part of 1.0 M hyamine [alkyl(C12-16)dimethylbenzylammonium chloride] with 1 part 100% ethanol) to which 2–3 drops of phenolphthalein had been added to generate a mauve colour change. The patients continued exhalation until the solution changed from mauve (alkaline) to clear (acid), indicating the trapping of approximately 2 mmol CO_2. The vials were then capped. The reference sample consisted of 4 ml hyamine solution mixed with 1 ml reference solution. The background capture solution contained 4 ml of hyamine solution and 1 ml of ethanol.

Once all the samples were collected, 10 ml of scintillant was added to each sample, and they were stored overnight at ~4°C in a black UV-proof plastic bag until counting. The vials were then counted in a liquid scintillation counter: counts were corrected to disintegrations per minute (dpm), using a standard quench programme.

(ii) Derivation of EMBT Parameters

Assuming an endogenous CO_2 production rate of 9 mmol/(kg·h) (a constant derived from sedentary individuals over a range of ages and weight) [44], the rate of $^{14}CO_2$ production was calculated as the % administered dose expired per minute where [4]:

$$^{14}\mathrm{CO_2flux}\ (\%/\mathrm{min}) = \frac{\mathrm{dpm_{breath\ sample}}}{\mathrm{dpm_{administered}}} \times \frac{9\ \mathrm{mmolCO_2/(kg \cdot h)}}{2\ \mathrm{mmolCO_2}} \times \frac{1\mathrm{h}}{60\ \mathrm{min}} \times \mathrm{bodyweight(kg)} \times 100\%$$

The $^{14}CO_2$ flux (i.e. % dose expired/min) was plotted as a function of time for each patient. The EBT parameters derived were the following: (1) $^{14}CO_2$ flux at 10 min ($CO_2f_{,(t=10)}$), (2) and 20 min ($CO_2f_{,(t=20)}$), (3) terminal rate constant of the $^{14}CO_2$ flux versus time curve, k_{CO2}, by log-linear extrapolation, (4) $AUC_{CO2,(0-\infty)}$ and $AUC_{CO2,(0-60)}$ of $^{14}CO_2$ flux versus time curve, from time = 0 to ∞ and to 60 min, respectively, estimated by the linear-trapezoidal rule. The analyses were performed using Microsoft Office Excel 2003 and WinNonLin Profession version 5.2. The results were summarised as mean, median, range and coefficient of variability (CV = [100% × (standard deviation)]/mean).

The antipyrine clearance test (ACT)

(i) Antipyrine administration

This was performed within one week of docetaxel administration as per Farrell et al. [10]. Each patient was given an oral dose of antipyrine, (Fernz Specialty Chemicals, Victoria, Australia), 10 mg/kg body weight, dissolved in 50 ml water. Blood samples were collected 0 (predose), 4 and 24 h following the dose, in the presence of lithium heparin and stored on ice. Plasma was separated from erythrocytes by centrifugation at 1,000×*g* for 10 min at 4°C and stored at −70°C until analysis.

(ii) Antipyrine analytical methodology

The plasma concentration of antipyrine was assayed using a modified version of a reported extraction and HPLC method [43].

(iii) Antipyrine pharmacokinetics (PK)

The antipyrine clearance (CL) was calculated as per Farrell et al. [10]. A log plasma concentration versus time curve was generated, and the elimination half-life ($t_{Ant:1/2}$) was calculated by least-square regression. The apparent volume of distribution $V_{Ant} = Dose/C_{Ant,t=0}$ was derived, where $C_{Ant,t=0}$ is the plasma concentration extrapolated back to $T = 0$ h. The antipyrine CL (CL_{Ant}, ml/min) = $(\ln[2] \times V_{Ant})/t_{Ant:1/2}$. The antipyrine CL was also corrected for body weight, i.e., $CL_{Ant,W} = CL_{Ant}/BW$, where BW = body weight.

Treatment programme

(1) Docetaxel administration

Docetaxel was administered either 3-weekly (75 mg/m^2, IV/1 h, every 21 days) or weekly (36 mg/m^2, IV/1 h, weekly by 6, q 8 weeks). Standard premedication comprised of dexamethasone 8 mg bid for 3 days, commencing on the day prior to chemotherapy.

(2) Docetaxel dose adjustments in subsequent courses

Dose adjustments for subsequent courses of docetaxel were made based upon the severity of toxicities as per the NCI-CTC version 3. For both regimens, dose reductions were at 25% increments based upon significant toxicities or

failure of adequate haematological recovery by time of the next dose. Treatment was continued until disease progression, intolerable toxicity or withdrawal of consent.

(3) Patient assessments

Patients treated every 3 weeks were reviewed on the day of each treatment. Blood samples were taken for haematological analysis 2–3 times per week and for biochemical analysis weekly in the first course and then on the days of chemotherapy. Toxicities were recorded weekly in the first course. Tumour response was assessed every 6 weeks using WHO criteria.

For those treated with weekly docetaxel, blood samples for haematological analysis were taken twice per week for the first 3 weeks and then weekly prior to each treatment. In the first course, patients were reviewed weekly for toxicities. Patients were reviewed at the commencement of each subsequent 8-week course, and tumour response was assessed every 8 weeks.

Neutropenia was described either by the ANC nadir counts or by the per cent change of ANC at the nadir relative to the baseline. The latter was calculated for the 3-weekly regimen patients, as the nadir was well defined following a single-drug exposure:

$$\%\text{Decrease} = 100\% \times \frac{(\text{ANC}_{\text{baseline}} - \text{ANC}_{\text{Nadir}})}{\text{ANC}_{\text{baseline}}},$$

where $\text{ANC}_{\text{baseline}}$ and $\text{ANC}_{\text{nadir}}$ = ANC at baseline or day 1 of therapy and at nadir, respectively.

(4) Docetaxel analytical methodology

Blood samples were taken for docetaxel PK during the first course of treatment. Blood samples were taken at predose (0 h), midinfusion (0.5 h), infusion end (1 h) and then at 5, 10, 30, 60, 90 min, 2, 4, 8 and 24 h following infusion end. Blood samples were collected on ice in the presence of lithium heparin. Plasma was separated from erythrocytes by centrifugation at $1{,}000 \times g$ for 10 min at 4°C and stored at −70°C until analysis. Docetaxel was assayed using a solid-phase extraction procedure followed by an isocratic reversed-phase HPLC method similar to that previously described [30].

(5) Docetaxel PK analysis

A log plasma concentration vs time curve was generated from the plasma concentration data. Pharmacokinetic parameters were derived by non-compartmental methods. Docetaxel PK parameters derived included the following (1) terminal elimination half-life: $t_{\text{Doc1/2}}$, (2) AUC ($\text{AUC}_{\text{Doc:0}-\infty}$) and (3) clearance: CL_{Doc}. The analyses were performed using Microsoft Office Excel 2003 and WinNonLin Profession version 5.2.

Statistical analysis

All 20 patients registered were included in these exploratory analyses. Baseline characteristics and treatment details were summarised using descriptive statistics, including mean, median, standard deviation and range for continuous data and counts and percentages for categorical data. The Pearson correlation coefficient was computed for EBT parameters, docetaxel PK, antipyrine CL versus baseline patient characteristics. Linear regression was used to examine the relationship between pairs of variables. The Wilcoxon rank sum test was used to compare the distribution of responses to docetaxel PK, antipyrine CL and EBT parameters according to gender and ECOG PS. The population was considered overall, and the impact of docetaxel schedule was also explored.

As this was an exploratory hypothesis generating study, no power calculation for sample size determination was carried out.

Statistical analyses were performed using S-Plus 2000 Professional software.

Results

Patients

Overall 20 patients were recruited; 19 had metastatic non-small cell lung cancer that progressed following initial platin-based chemotherapy. Their demographics were typical for this population (Table 1).

Treatment delivery

Overall 13 of 20 patients were treated with the 3-weekly docetaxel regimen: one patient had come off study, due to lack of cooperation with the EBT, and another 2 patients had changed over to the weekly regimen, due to intolerance. The treatment delivery is summarised in Table 2. Overall 7 patients were treated with the weekly regimen.

Only 2 of the 20 had a dose reduction after cycle 1, the first by grade 3 oesophagitis/neutropenia in cycle 1 and the second by significant arthralgia and performance status decline in cycle 1.

Docetaxel pharmacodynamic endpoints: toxicity and response

The best radiological responses are summarised in Table 2, where overall 30% of patients achieved stable disease. Generally, the chemotherapy was well tolerated. The major haematological toxicity was neutropenia: (1) 3-weekly

Table 1 Patient demographics

Parameter	Mean (range)	% ($N = 20$)
Male:Female	12:8	60:40
Age (years)	62 (41–77)	
Body surface area (m^2)	1.77 (1.44–2.07)	
ECOG PS distribution		
0	0	0
1	9	45%
2	11	55%
Malignancy		
Advanced non-small cell lung cancer	19	95
Advanced breast cancer	1	5
Bilirubin (μmol/ml)	6.35 (3–15)	
ALP (U/L)	98.9 (10–237)	
ALT (U/L)	25.7 (6–95)	
AST (U/L)	23 (9–167)	
Protein (g/l)	68.7 (51–76)	
Albumin (g/l)	34.5 (25–41)	
Hepatic synthetic markers		
Serum transferrin (2–3.6 g/l) ($n = 18$)	2.3 (1.6–3.0)	
INR (0.8–1.2) ($n = 14$)	1.0 (0.8–2.3)	
Prothombin time (11.8–14.6 s) ($n = 6$)	17.4 (11.1–30.3)	
C-reactive protein (0–10 mg/l) ($n = 11$)	59.5 (1–303)	

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *ALT* aspartate aminotransferase

Table 2 Docetaxel treatment delivery, treatment-related toxicity and response to therapy

Parameter	Mean (Range)	% ($N = 20$)
Docetaxel treatment delivery	13: 7	65:35
3 weekly: weekly		
3-weekly regimen (75 mg/m^2)		
Dose (mean) (mg)	130.4	
No. Courses	2.8 (1–7)	
Weekly regimen (35 mg/m^2)		
Dose (mean) (mg)	64.4	
No. courses	1.3 (1–3)	
Overall radiological response[a]		
Partial response	1	5
Stable disease	6	30
Progressive disease	13	65
Reason off treatment		
Progressive disease	15	75
Toxicity	3	15
Completed therapy	2	10

Myelosuppression[b] ($n = 12$)	Mean (Range)	CV[c]
Baseline ANC[c]	5.9 (1.2–10.3)	45.5
Nadir ANC	1.6 (0.04–9.1)[e]	150.6
% Decrease at nadir relative to baseline[d]	76.3 (4.9–9.3)	32.2

[a] As per WHO criteria

[b] $N = 12$ patients who received docetaxel every 3 weeks, as there was a clearly defined nadir post-exposure relative to the patients treated with the weekly regimen

[c] *ANC* absolute neutrophil counts, *SD* standard deviation, *CV* coefficient of variation = 100 × (standard deviation/mean)

[d] % Decrease at nadir relative to baseline = $100 \times (ANC_{baseline} - ANC_{Nadir})/ANC_{baseline}$, where $ANC_{baseline}$ = ANC at baseline or day 1 of therapy where available and ANC_{Nadir} = ANC at nadir

[e] Nadir on day 9 (mean) (range days 7–15)

regimen- grade 4 in 2 patients and grade 3 in 5 and (2) weekly regimen: grade 3 in 1. There were no episodes of febrile neutropenia.

Docetaxel PK

The PK parameters are summarised in Table 3. As expected, there were no significant differences between the 3-weekly and weekly regimens for CL_{Doc}, $t_{Doc1/2}$ or Vd_{Doc}. The inter-patient variability for these parameters, as reflected by the coefficient of variation (CV), ranged from 25.1 to 38.6% and 26.3 to 46.9% for the 3-weekly and weekly regimens, respectively.

In vivo probes

The results of the EBT and the antipyrine CL test (ACT) are summarised in Table 3. With regard to the EBT, the inter-patient variability was wide ranging from 22.1% for k_{CO2} to 106% for $CO_2f_{,(t\ =\ 10)}$: much wider than the docetaxel PK mentioned earlier. There was a very good linear correlation between $AUC_{CO2,f(0-\infty)}$ and $CO_2f_{,(t\ =\ 20)}$ ($R^2 = 0.84$) and $CO_2f_{,(t\ =\ 10)}$ ($R^2 = 0.89$), similarly between $AUC_{CO2,f(0-60)}$ and $CO_2f_{,(t\ =\ 20)}$ or $CO_2f_{,(t\ =\ 10)}$ ($R^2 = 1.0$ and $R^2 = 0.81$, respectively).

With regard to the ACT, as per Table 3, the inter-patient variability for the CL_{Ant} and CL_{AntW} was 37.5 and 34.7%, respectively. There was a good linear correlation between the 2 parameters ($R^2 = 0.72$).

The relationship between docetaxel PK and patient demographics

For the entire cohort, there was a significant correlation between docetaxel $AUC_{Doc:0-\infty}$ and each of bilirubin, AST and protein ($P < 0.031$) and also a significant linear relationship between log(AST) and $AUC_{Doc:0-\infty}$ ($P < 0.001$,

Table 3 Docetaxel pharmacokinetic, C^{14}-erythromycin breath test ($n = 19$) and antipyrine clearance test ($n = 20$)-derived parameters

Parameter	Mean	Range	CV[a]
Docetaxel PK[a]			
3 weekly (75 mg/m^2) ($N = 12$)			
$T_{Doc½}$ (h)	13.69	8.45–19.1	25.1
$AUC_{Doc:0-\infty}$ (μg h/ml)	2.82	1.22–4.33	28.3
CL_{Doc} (L/h)	50.32	30–90.1	37.6
VD_{Doc} (L)	974.3	502–1836.4	38.6
Weekly (36 mg/m^2) ($N = 7$)			
$T_{Doc½}$ (h)	11.1	4.24–20.0	46.9
$AUC_{Doc:0-\infty}$ (μg h/ml)	0.99	0.55–1.31	26.3
CL_{Doc} (L/h)	68.94	47.7–105.7	28.3
VD_{Doc}(L)	1,041.0	391.8–1373.7	35.8
C^{14}-erythromycin breath test			
$CO_2f_{,(t\ =\ 10)}$ (%/min)	0.051	0.006–0.262	106.0
$CO_2f_{,(t\ =\ 20)}$ (%/min)	0.052	0.007–0.21	82.04
k_{CO2} (min^{-1})	0.007	0.004–0.011	22.1
$AUC_{CO2,f(0-60)}$	2.64	0.39–10.4	79.1
$AUC_{CO2,f(0-\infty)}$	7.90	1.09–24.9	70.85
Antipyrine clearance test			
CL_{Ant} (ml/min)	35.81	20.7–70.8	37.5
$CL_{Ant,W}$ (ml/(min kg)	0.53	0.26–0.88	34.7

[a] $\%CO_{2,(t\ =\ 10)}$),$\%CO_{2,(t\ =\ 10)} = {}^{14}CO_2$ excretion or flux (i.e. % dose expired per minute) at $t = 10$ and 20 min, respectively; k_{CO2} = terminal rate constant of decline of the $^{14}CO_2$ excretion (i.e. % dose expired per minute) versus time curve; $AUC_{CO2,(0-\infty)}$ and $AUC_{CO2,(0-60)}$ = Area under the $^{14}CO_2$ excretion (i.e. % dose expired per minute) versus time curve, from time = 0 to ∞ and 0 to 60 min, respectively; *CV* coefficient of variation, CL_{Ant} (ml/min) antipyrine clearance, as per Farrell [10], $CL_{Ant,W}$ antipyrine CL corrected for body weight

$R^2 = 69.7\%$). For CL_{Doc}, there was a significant inverse relationship with AST ($P = 0.036$), which was also linear ($P = 0.009$, $R^2 = 44.46\%$). For the 3-weekly regimen cohort, there were similar relationships. $AUC_{Doc:0-\infty}$ and both AST and Albumin ($P < 0.041$) and both were linear ($P < 0.041$). Similarly, there was a significant inverse relationship between CL_{Doc} and AST ($P = 0.006$). For patients receiving the weekly regimen, there was an inverse correlation between CL_{Doc} and Age ($P = 0.047$).

The relationship between antipyrine clearance and patient demographics, docetaxel PK and toxicity

(1) Patient Demographics: (Table 4)

For the cohort overall, serum ALP was significantly correlated with CL_{Ant} ($P = 0.008$) and CL_{AntW} ($P = 0.049$). For the patients receiving the 3-weekly regimen, CL_{Ant} was significantly correlated with ALP ($P = 0.021$) and BSA ($P = 0.041$), with the relationships being linear for both ($P = 0.021$, $R^2 = 42.81\%$ and $P = 0.041$, $R^2 = 32.84\%$, respectively).

Similarly, as for CL_{Doc}, for the patients receiving the weekly regimen, there was a significant inverse correlation between age and both CL_{Ant} ($P = 0.006$) and CL_{AntW} ($P = 0.044$).

(2) Docetaxel PK (Table 5)

(a) All patients and patients in 3-weekly docetaxel cohort: for the entire cohort (Fig. 1a) and the 3-weekly cohort, there was no correlations between the ACT and docetaxel PK parameters.

(b) Patients in the weekly docetaxel cohort: There was a significant inverse correlation between $AUC_{Doc:0-\infty}$ and CL_{Ant} ($P = 0.017$), which was also linear in nature ($P = 0.017$, $R^2 = 71\%$), similarly between $AUC_{Doc:0-\infty}$ and CL_{AntW} ($P = 0.028$), ($P = 0.028$, $R^2 = 65.4\%$). One point had high leverage on both fitted lines ($AUC_{Doc:0-\infty} = 0.55$, $CL_{Ant} = 50.3$, $CL_{AntW} = 0.88$): if this point was omitted, then the relationships were no longer significant ($P = 0.197$, $R^2 = 37.4\%$, and $P = 0.361$, $R^2 = 20.9\%$, respectively).

There was also a significant correlation between CL_{Doc} and CL_{Ant} ($P = 0.007$), which was also linear ($P = 0.007$, $R^2 = 79.47\%$, Fig. 1b). One point, corresponding to the same patient earlier, had a high leverage and if omitted the relationship was no longer significant ($P = 0.223$, $R^2 = 34.1\%$).). Similarly, the relationship between CL_{Doc} and CL_{AntW} was also significant ($P = 0.039$) and also linear in nature ($P = 0.028$, $R^2 = 65.41\%$).

(3) Docetaxel Toxicity:

There was no correlation between CL_{Ant} and CL_{AntW} and the ANC nadir counts or %decrease in ANC at the nadir relative to baseline for the patients who received the 3-weekly regimen.

The relationship between EBT and patient demographics, docetaxel PK and toxicity

(1) Patient Demographics (Table 4)

For the entire cohort and for those who received the 3-weekly or weekly regimen, there was a significant correlation between ALP and each of $AUC_{CO2,f(0-60)}$, $AUC_{CO2,f(0-\infty)}$, $CO_2f_{,(t\ =\ 10)}$ and $CO_2f_{,(t\ =\ 20)}$. For the weekly cohort: a significant correlation between ALT and $CO_2f_{,(t\ =\ 10)}$ ($P = 0.05$) was also observed.

(2) Docetaxel Pharmacokinetics and Toxicity

For the entire cohort, regardless of regimen, there were no correlations between the EBT and docetaxel PK

Table 4 Correlation between antipyrine clearance and erythromycin breath test parameters with serum hepatic biochemistries and patient demographics for all patients

Parameter	Pearson correlation (P value)[a] All patients						
	Antipyrine clearance		Erythromycin breath test				
	CL_{Ant}	CL_{AntW}	$AUC_{CO2,f(0–60)}$	$AUC_{CO2,f(0–\infty)}$	$CO_2f_{,(t = 10)}$ (%/min)	$CO_2f_{,(t = 20)}$ (%/min)	k_{CO2} (min^{-1})
Bilirubin (μmol/l)	−0.043 (0.857)	−0.042 (0.861)	−0.195 (0.423)	−0.247 (0.308)	−0.136 (0.580)	−0.185 (0.447)	0.072 (0.771)
ALP (U/L)	**0.589 (0.008)**	**0.457 (0.049)**	0.771 (0.0)	**0.629 (0.005)**	0.781 (0.0)	0.768 (0.0)	0.249 (0.319)
ALT (U/L)	0.029 (0.905)	−0.013 (0.955)	0.101 (0.682)	0.079 (0.748)	0.105 (0.669)	0.116 (0.636)	0.005 (0.983)
AST (U/L)	−0.044 (0.881)	0.027 (0.927)	−0.356 (0.212)	−0.403 (0.153)	−0.308 (0.284)	−0.345 (0.227)	0.023 (0.937)
Protein (g/L)	0.289 (0.216)	0.193 (0.416)	0.324 (0.175)	0.360 (0.130)	0.288 (0.233)	0.335 (0.161)	−0.204 (0.403)
Albumin (μmol/l)	−0.023 (0.924)	−0.205 (0.386)	0.365 0.124)	0.414 (0.078)	0.292 (0.224)	0.366 (0.123)	−0.306 (0.203)
BSA (m^2)	0.276 (0.239)	−0.237 (0.314)	0.418 (0.075)	0.415 (0.077)	0.335 (0.161)	0.436 (0.062)	−0.272 (0.259)
Age (years)	−0.302 (0.195)	−0.254 (0.28)	−0.004 (0.987)	−0.110 (0.655)	−0.045 (0.856)	−0.006 (0.980)	0.250 (0.302)

Significant Pearson coefficient and two-sided P values < 0.05 are bolded

[a] Sig. (2-tailed)

Table 5 Correlation between antipyrine clearance and erythromycin breath test and with docetaxel pharmacokinetics for all patients and for those treated with the 3-weekly and weekly regimens

Parameter	All patients		3 weekly (75 mg/m^2)		Weekly (35 mg/m^2)	
	Pearson correlation (P value)[a] ($N = 19$)		Pearson correlation (P value)[a] ($N = 12$)		Pearson correlation (P value)[a] ($N = 7$)	
	$AUC_{Doc:0–\infty}$ (μg h/ml)	CL_{Doc} (L/h)	$AUC_{Doc:0–\infty}$ (μg h/ml)	CL_{Doc} (L/h)	$AUC_{Doc:0–\infty}$ (μg h/ml)	CL_{Doc} (L/h)
Erythromycin breath test						
$AUC^{b}_{CO2,f(0–60)}$	0.111 (0.652)	−0.048 (0.846)	0.067 (0.836)	−0.059 (0.856)	−0.058 (0.902)	0.238 (0.608)
$AUC_{CO2,f(0–\infty)}$	−0.044 (0.857)	0.124 (0.612)	0.093 (0.774)	−0.104 (0.747)	−0.344 (0.45)	0.536 (0.215)
$CO_2f_{,(t = 10)}$ (%/min)	0.225 (0.353)	−0.114 (0.642)	0.062 (0.848)	−0.035 (0.915)	−0.126 (0.788)	0.149 (0.749)
$CO_2f_{,(t = 20)}$ (%/min)	0.128 (0.603)	−0.053 (0.829)	0.064 (0.844)	−0.05 (0.876)	−0.046 (0.921)	0.238 (0.607)
k_{CO2} (min^{-1})	0.07 (0.775)	−0.093 (0.705)	−0.368 (0.239)	0.453 (0.14)	0.477 (0.279)	−0.694 (0.084)
Antipyrine clearance						
CL_{Ant} (ml/min)	0.184 (0.451)	0.228 (0.349)	−0.046 (0.886)	0.224 (0.483)	**−0.843 (0.017)**	**0.891 (0.007)**
CL_{AntW} (ml/min/kg)	0.132 (0.59)	0.256 (0.29)	−0.209 (0.14)	0.26 (0.415)	**−0.809 (0.028)**	**0.778 (0.039)**

Significant Pearson coefficient and two-sided P values < 0.05 are bolded

[a] Sig. (2-tailed)

[b] $\%CO_{2,(t = 10)}$),$\%CO_{2,(t = 10)} = {}^{14}CO_2$ excretion or flux (i.e. % dose expired per minute) at $t = 10$ and 20 min, respectively; k_{CO2} = terminal rate constant of decline of the $^{14}CO_2$ excretion (i.e. % dose expired per minute) versus time curve; $AUC_{CO2,(0–\infty)}$ and $AUC_{CO2,(0–60)}$ = Area under the $^{14}CO_2$ excretion (i.e. % dose expired per minute) versus time curve, from time = 0 to ∞ and 0 to 60 min, respectively; *CV* coefficient of variation, CL_{Ant} (ml/min) antipyrine clearance, as per Farrell [10], $CL_{Ant,W}$ antipyrine CL corrected for body weight

parameters (Table 5). Similarly, there were no correlations observed between the EBT parameters and the ANC nadir counts or %decrease in ANC at the nadir relative to baseline for the patients receiving the 3-weekly regimen.

Discussion

Given the well-known weaknesses of BSA-based dosing of cytotoxics, alternative dosing methods are required to reduce the inter-patient variability in drug exposure and

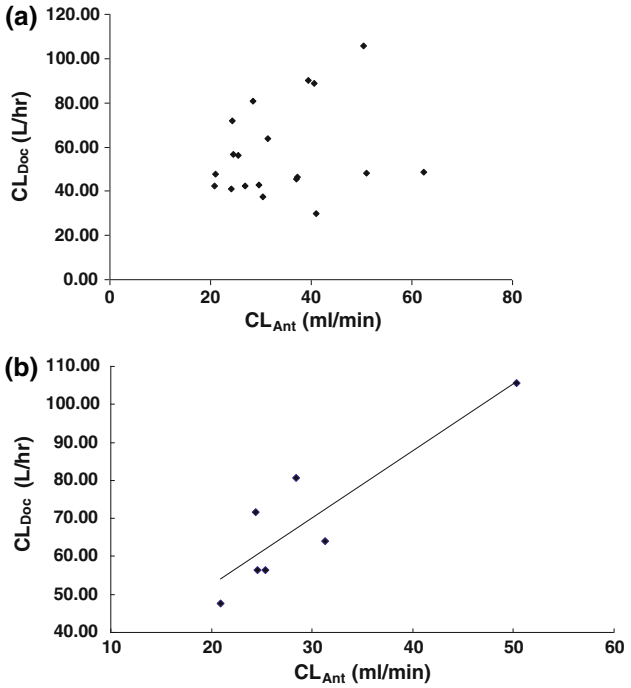

Fig. 1 The relationship between docetaxel PK parameters and the antipyrine CL test. **a** Docetaxel CL (CL_{Doc}) and antipyrine CL (CL_{Ant})for all patients ($N = 19$). **b** Docetaxel CL (CL_{Doc}) and antipyrine CL (CL_{Ant}) for all patients receiving the weekly regimen ($N = 7$) ($CL_{Doc} = 16.96 + 1.77 \times CL_{Ant}$, ANOVA, $P = 0.007$, $R^2 = 79.47\%$)

toxicity and hence optimise the therapeutic index. Phenotyping of relevant metabolic/excretory enzymes for cytotoxics is one such method that is dependant on well-characterised pathways and probe quality. However, different probes of the same pathway do not provide the same correlates with drug PK. Inclusion of relevant gene polymorphisms may potentially also improve these models. These tests also need to be widely applicable, provide real-time results and be cost-effective. The aims of this exploratory trial were thus to determine the correlation between 2 distinct validated in vivo probes of hepatic metabolic function, the EBT and the ACT, and docetaxel PK and toxicity. In addition, we attempted to explore their relative utility between patients receiving the commonly used docetaxel regimens.

It is noted form the outset that this study must be considered in light of several caveats. First is the sample size ($n = 20$), a pragmatic figure derived from a single centre: overall 7 were treated with weekly docetaxel. Second, the docetaxel PK sampling schedule in this study stopped at 24 h post-infusion end, and in other studies, extended sampling beyond 24-h has confirmed a prolongation of the terminal half-life and reduced CL_{Doc} [18].

Third, the ACT itself is an oral test hence it theoretically may be impacted on by first-pass metabolism within the gastrointestinal tract relative to intravenous docetaxel. However, studies in healthy volunteers have shown that antipyrine given as an oral aqueous solution has complete bioavailability, and there were no significant PK differences between oral and IV administration, implying negligible first pass effect [7]. Also, despite antipyrine being a substrate for several CYP-P450 s, it is predominantly metabolised by CYP3A4 [8].

In the cohort examined here, as expected, the CL_{Doc} was similar between the 3-weekly and weekly regimen (Table 3), with the range confirmed by others [2, 5, 20, 35, 38, 45]. The primary aim of this study was to correlate the metabolic probes EBT and ACT with docetaxel PK and PD, and thus, each will be considered in turn. With regard to the EBT, the parameters assessed varied approximately 30–40 × within the cohort (Table 3), as reported in those with normal hepatic biochemical function [20]. There was a significant correlations between ALP and several EBT flux parameters and for the weekly cohort between ALT and $CO_2f_{,(t\ =\ 10)}$ (Table 4).

In this study, we failed to identify a correlation between docetaxel PK and the EBT parameters, regardless of regimen. The EBT has been inconsistently correlated with docetaxel clearance (CL_{Doc}) [1, 3, 20, 21, 38] and, similarly, did not correlate with CL_{Doc} in another study with the weekly regimen [35]. A population model has also evaluated the relationship between CYP3A4 activity (using the EBT) and CL_{Doc} in 77 patients with varying degrees of liver function [21]. Unbound CL_{Doc} was lower and more variable in patients with liver function abnormalities. Population PK modelling in patients with liver dysfunction demonstrated that the covariates evaluated accounted for 83% of variability in CL_{Doc}: with CYP3A4 activity accounting for 47% of this variation [21]. Though in patients with normal liver function, the same covariates accounted for only 23% of CL_{Doc} variability [21].

Hence, based on these population approaches, it appears the utility of the EBT may actually lie in identifying safe docetaxel doses for patients with liver function abnormalities rather than those with normal function as seen in the cohort examined here [21]. The trial reported here required patients to have normal serum hepatic biochemistries. It is unclear though that inclusion of patients with biochemical hepatic impairment, in order to expand the range of observed docetaxel CLs, would enable significant correlations to be observed. Other causes, however, may include the small patient cohort and the limited PK sampling.

It must be noted that the measurement of the exhaled $^{14}CO_2$ provides an indirect quantification of hepatic CYP3A4 activity [24, 42], and it may in fact reflect hepatic ABC-B1 function [23, 36, 37]. Polymorphisms in the CYP3A4/5 and transporters genes also have an impact on CL_{Doc}. In 93 Caucasians, the simultaneous presence of the

CYP3A4*1B and CYP3A5*1A alleles was associated with a 64% increase in CL_{Doc} ($P = 0.0015$), independent of the CYP3A activity (as determined by the EBT) [1]. The EBT $^{14}CO_2$ flux was found to be decreased by the rifampicin-induced inhibition of OATP and increased by the lansoprazole-induced inhibition of ABC-B1 [12]. Thus, the interpretation of the EBT as a measure of CYP3A4 metabolism, and drug CL, requires the careful consideration of relevant transporter interactions and haplotypes [12]. The EBT methodology also presents logistical issues in terms of its applicability in the general clinical setting [9].

Given these limitations of the EBT, midazolam being a pure CYP3A4 substrate, and whose drug handling is unaffected by hepato-biliary transporter activity, may represent a practical alternative probe. The midazolam clearance test, has been well validated as a CYP3A4/5 probe and been evaluated for possible correlations with docetaxel CL [14]. In this study, midazolam was administered intravenously to these patients at least 2 days before docetaxel treatment. Midazolam clearance ($P = 0.001$) was the strongest predictor of docetaxel CL on multiple linear regression analysis, Karnofsky performance status (KPS) ($P = 0.034$) being the only other significant predictor ($R^2 = 0.68$, $P < 0.001$). The model for docetaxel clearance was as follows: docetaxel CL $= -6171.0 + 22.3 \times$ (midazolam clearance) $+ 236.2 \times$ KPS [14].

With regard to the antipyrine clearance test (ACT), the range of CL_{Ant} values observed in this study was similar to that in two prior studies of cancer patients receiving taxanes [27, 28] (Table 3). With regard to the study reported here, for the overall cohort, CL_{Ant} was significantly correlated with ALP ($P < 0.05$), similarly for those receiving the 3-weekly regimen (Table 4). The correlation of antipyrine metabolism with liver function and its impact by malignancy have been investigated by others. In a large study, the antipyrine CL was evaluated in 518 subjects: the cohort comprised of healthy volunteers and patients with liver metastases or chronic active hepatitis/cirrhosis. The CL_{AntW} in patients with liver metastases (0.426 ± 0.174 ml/min/kg) was similar to that of the healthy group [16]. However, antipyrine CL values in cancer patients [31], and those specifically with hepatic metastases [15], are inconsistent relative to those in the healthy volunteers. In term of other cytotoxics, the antipyrine elimination rate has been correlated with the paclitaxel elimination rate constant in 21 patients ($P < 0.05$) [28]. The PK of adriamycin, its metabolites, and that of antipyrine were studied in 36 patients including 17 with moderate hepatic tumour involvement [32]. The adriamycin CL and half-life correlated significantly ($P < 0.01$, respectively) with the corresponding antipyrine PK parameters, but not with the usual liver function parameters [32].

One of the primary aims of this study was to identify correlations between the ACT and docetaxel PK. Only for the patients receiving weekly docetaxel, there was a significant correlation and linearity between CL_{Doc} and CL_{Ant} and CL_{AntW} ($P = 0.007$ and $P = 0.039$, respectively).(Table 4; Fig. 1b) The relationships were influenced by one point that had high leverage on both lines. The patient corresponding to this point was a 41-year-old woman, ECOG PS 2, with advanced lung cancer (without hepatic metastases) who received weekly docetaxel. Her baseline serum hepatic biochemistries were within normal limits, but of INR of 2.3 and albumin of 35 g/l. She was not taking relevant medications. Her $CL_{Doc} = 105.69$ l/h and corresponding low AUC, though are within the expected range in cancer patients: hence, she represented a true data point [11]. If this point was omitted, then the relationship was no longer significant ($P = 0.223$); however, at least 30% of the CL_{Doc} variability was still accounted for by CL_{Ant}. Nevertheless, the result thus must be interpreted with caution given the caveats above: in particular, the small sample size for the weekly cohort and the linear PK of docetaxel, where a correlation should also be expected for the 3-weekly regimen.

There has been extensive literature correlating docetaxel PK with myelosuppression [5, 6, 33]. Significant PD covariates have included serum α_1-acid glycoprotein, prior therapy [33], age $\geq$ 65 years [40], and the germline GSTP1*A/*B and ABCB1 3435TT genotypes [41]. In this study, there was no correlation of docetaxel toxicity, in particular neutropenia, with EBT or ACT parameters. It must be noted that the ANC nadir post-single-drug exposure was only clearly defined for the 3-weekly regimen cohort ($n = 13$). The ACT has been correlated with the risk of neutropenia in 25 patients with advanced lung cancer treated with docetaxel and cisplatin [27]. On multiple regression analysis, the antipyrine disappearance rate (ADR) and α_1-acid glycoprotein independently correlated with the neutropenia nadir. In addition, grades 3–4 neutropenia was observed in 7 of 9 'low ADR' patients (77%), versus in 5 of 16 'high ADR' patients (31%) [27].

The correlation of the EBT parameters with cytotoxic-induced toxicity is contradictory. In the study by Hirth et al. [20], 21 heavily pretreated patients received docetaxel (100 mg/m^2) and underwent the EBT. Multivariate analysis showed that the ln(%^{14}C exhaled in 1 h) and albumin accounted for 72% of the CL_{Doc} variation. In that study, two patients requiring hospitalisation with the severest toxicities (mucositis/sepsis/neutropenia) were those with the lowest EBT value and CL_{Doc} results [20]. The utility of the EBT to predict toxicity has not been confirmed for other CYP3A4 cytotoxic substrates. In a study of 20 elderly patients treated with weekly docetaxel, there was an association between the EBT results and drug PK

variables; however, there was no association between the EBT or drug PK parameters with frequency of grade 3 or greater toxicity [22].

In conclusion, this exploratory study has evaluated the comparative utility of antipyrine clearance test and the erythromycin breath test to predict docetaxel PK and PD. With the caveat of the small sample size, antipyrine clearance may correlate with docetaxel CL in patients, where the agent is given weekly. Further evaluation of the antipyrine clearance test together with the incorporation of other covariates of drug handling/toxicity (including inflammatory markers, α_1-acid glycoprotein and pharmacogenomics) is warranted in this setting.

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