Cancer Science
Japanese Cancer Association JCA
Open Access

Dose modifications in Asian cancer patients with hepatic dysfunction receiving weekly docetaxel: A prospective pharmacokinetic and safety study

Nicholas Li-Xun Syn,[1,2] Lingzhi Wang,[1,2,3] Andrea Li-Ann Wong,[1] Mu-Yar Soe,[1] Benjamin Chuah,[1] Daniel Chan,[1] Sing-Huang Tan,[1] Ross Andrew Soo,[1,2] Soo-Chin Lee,[1,2] Boon-Cher Goh[1,2,3] and Wei-Peng Yong[1,2]

[1]Department of Haematology-Oncology, National University Cancer Institute, Singapore; [2]Cancer Science Institute, Centre for Translational Medicine, National University of Singapore, Singapore; [3]Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Key words

Antineoplastic combined chemotherapy protocols, biomarkers, neutropenia, pharmacokinetics, taxoids

Correspondence

Wei-Peng Yong, Department of Haematology-Oncology, National University Cancer Institute, Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 7, Singapore 119228, Singapore.
Tel: +65-6772-4140; Fax: +65-6772-5680;
E-mail: wei_peng_yong@nuhs.edu.sg

Funding Information

National Medical Research Council, Singapore.

Received October 20, 2015; Revised December 2, 2015; Accepted December 5, 2015

Cancer Sci **107** (2016) 173–180

doi: 10.1111/cas.12856

Hepatic dysfunction may modify the safety profile and pharmacokinetics of docetaxel in cancer patients, but no validated guideline exists to guide dose modification necessitated by this uncommon comorbidity. We carried out the first prospective study of a personalized dosage regimen for cancer patients with liver dysfunction treated with docetaxel. Weekly dosages were stratified by hepatic dysfunction classification as such: Category 1, normal; Category 2, mild – alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase ≤5× upper limit of normal (ULN), and total bilirubin within normal range; and Category 3, moderate – any alkaline phosphatase, and aspartate aminotransferase or alanine aminotransferase ≤5–10× ULN, and/or total bilirubin ≤1–1.5× ULN. Category 1, 2 and 3 patients received starting dosages of 40, 30, and 20 mg/m^2 docetaxel, respectively. Pharmacokinetics were evaluated on day 1 and 8 of the first treatment cycle, and entered into a multilevel model to delineate interindividual and interoccasion variability. Adverse event evaluation was carried out weekly for two treatment cycles. We found that docetaxel clearance was significantly different between patient categories ($P < 0.001$). Median clearance was 22.8, 16.4, and 11.3 L/h/m^2 in Categories 1, 2, and 3, respectively, representing 28% and 50% reduced clearance in mild and moderate liver dysfunction patients, respectively. However, docetaxel exposure (area under the concentration–time curve) and docetaxel-induced neutropenia (nadir and the maximum percentage decrease in neutrophil count) were not significantly different between categories. Median area under the concentration–time curve was 1.74, 1.83, and 1.77 mg·h/L in Categories 1, 2, and 3, respectively. The most common Grade 3/4 toxicity was neutropenia (30.0%). An unplanned comparison with the Child–Pugh and National Cancer Institute Organ Dysfunction Working Group grouping systems suggests that the proposed classification system appears to more effectively discriminate patients by docetaxel clearance and dose requirements. (ClinicalTrials.gov registration no. NCT00703378).

Hepatic dysfunction is a rare comorbidity affecting approximately 0.2% of cancer patients,[1] making it particularly challenging to accrue patients with hepatic dysfunction in oncology trials that assess its effects on the pharmacokinetics and safety profile of chemotherapeutic agents. The paucity of guidance on the treatment of this patient subpopulation can be a real practice issue in clinical oncology; many drugs that form the backbone of chemotherapy have narrow therapeutic windows and are often dosed close to maximally tolerable levels. Unacceptable toxicities can quickly set in if the implications of a reduced hepatic metabolic capacity are not properly regarded, as hepatic drug biotransformation is the predominant route of elimination for many cytotoxic agents.[2] We therefore propose that it may be helpful to risk-stratify cancer patients before starting them on a personalized dosage regimen.

Docetaxel is an antitubulin widely found in combination regimens for multiple tumor types, inducing cell cycle arrest and pro-apoptotic pathways by promoting microtubule assembly and blocking their disassembly. As a single agent, it has been used in the second and subsequent line settings for advanced and metastatic breast cancer and non-small-cell lung cancer. Docetaxel undergoes extensive hepatic metabolism through the CYP3A drug-metabolising pathway,[3] and therefore can be expected to show altered disposition in the setting of liver dysfunction.[4] In observational and retrospective studies, docetaxel clearance is reduced by 12–38% in patients with elevated plasma levels of TB and/or transaminases.[5,6] Bruno *et al.*[7] showed that clearance was reduced by 27% in patients with ALT or AST >1.5× ULN and ALP >2.5× ULN. In a previous issue in this journal, Minami *et al.*[6] recommended

dose reduction by approximately 20% and 40% in patients with grade 2 and 3 elevations of transaminases and elevated ALP based on population PK modeling. Importantly, as Minami and colleagues noted, this recommendation needs to be validated prospectively.

The Child–Pugh[8] and NCI-ODWG[9] grouping systems are established classification criteria for grading the severity of liver dysfunction. Both grouping systems rely on liver function markers to risk-stratify patients. However, based on several aforementioned studies that have identified important covariates predictive of docetaxel PK, we observed that the components used to compute Child–Pugh and NCI-ODWG scores as well as the cut-off values for stratification may not be adequately sensitive for patients treated with docetaxel. For example, the Child–Pugh score includes presence of ascites, encephalopathy, and INR elevation, which are not well-established predictive covariates of docetaxel PK. The NCI-ODWG grouping emphasizes the use of TB levels to classify the severity of hepatic dysfunction, but does not take into account other predictive factors such as ALT and ALP. These in theory could lead to inappropriate risk stratification. Another limitation is that both criteria provide little guidance, in the way of specific dosing recommendations, on how to modify chemotherapy regimens.

Due to higher response rates in Asian patients treated with docetaxel-containing regimens compared with Caucasian patients,[10] docetaxel is routinely prescribed in the Asian setting. There remains a continued need to seek optimized doses based on patient status.[11] We therefore carried out the first prospective clinical trial to investigate the utility of a dosing nomogram for guiding dose modifications in Asian cancer patients with hepatic dysfunction. The secondary objective was to characterize the PK of weekly docetaxel in this subpopulation. An unplanned analysis was carried out to compare the discriminatory power of the proposed risk-stratification system with Child–Pugh and NCI-ODWG grouping systems.

Patients and Methods

Patient selection. Patients with a histologically or cytologically confirmed malignancy for which docetaxel was indicated were identified and recruited from the National University Hospital, Singapore on an outpatient basis between 2006 and 2011. Other eligibility criteria were as follows: grade <1 toxic effects from any prior surgery, radiotherapy, or chemotherapy with the exception of alopecia, fatigue, nausea, and asthenia according to the NCI Common Toxicity Criteria 3.0, Eastern Cooperative Oncology Group performance status ≤2, normal renal and marrow function (white blood cell count ≥3000/μL, absolute neutrophil count ≥1500/μL, platelets ≥100 000/μL, hemoglobin ≥7 g/dL, and creatinine ≤1.5× ULN). Patients were excluded from the study if they received chemotherapy or radiotherapy within 4 weeks or medications known to be CYP3A substrates within 1 week prior to study enrolment, or had uncontrolled intercurrent illnesses including active infection with hepatitis B or C. The study is registered at ClinicalTrials.gov (NCT00703378), and the study protocol was approved by the Domain Specific Review Board, National Healthcare Group, Singapore. All patients provided written, informed consent prior to study entry.

Treatment and follow-up. Baseline evaluation included a physical examination and evaluation of performance status within 4 weeks of enrolment and full blood count including differential counts and platelets, and chemistries within 7 days of docetaxel treatment. Hematology, chemistries, and an adverse event evaluation were carried out weekly at each course of infusion. Adverse events were registered according to the NCI Common Terminology Criteria for Adverse Events 3.0.

Patients were assigned to Category 1 if they had normal liver function, Category 2 if they had mild liver dysfunction, which we defined as having AST and/or ALT and ALP up to 5× ULN, and TB within normal limits, or Category 3 if they had moderate liver dysfunction, which entailed any ALP, and AST or ALT 5–10× ULN, and/or TB 1–1.5× ULN with elevated liver enzymes. Premedication with dexamethasone 8 mg oral tablets b.i.d. was given 24 h prior to the first docetaxel (Taxotere; Aventis Pharma SA, Antony Cedex, France) infusion and for the next 48 h. A single 8-mg dose of dexamethasone was given 1 h prior to subsequent docetaxel infusions. The patients also received i.v. ondansetron 8 mg 1 h before docetaxel infusion. Patients in Categories 1, 2, and 3 received initial docetaxel doses of 40, 30, and 20 mg/m^2, respectively, given over a 1-h infusion on days 1 and 8 of a 21-day cycle for two cycles. Subsequent doses within a cycle were modified based on platelet count and ANC, and were reduced by 25% if ANC was 1000–1450/μL, or omitted if platelets ≤100 000/μL and/or ANC ≤1000/μL. Docetaxel doses were reduced by 25% in the subsequent cycle if the patients experienced dose omission during the previous cycle. Up to two dose reductions were permitted. Granulocyte-colony stimulating factor was permitted only in the event of prolonged grade 4 neutropenia for more than 7 days or neutropenic fever.

Pharmacokinetic and statistical analysis. Data from our previous study[12] was used to design a D-optimal sampling schedule in ADAPT II.[13] Serial blood samples were drawn into heparin-containing vacutainers on days 1 and 8 of cycle 1 at 0, 0.25, 1.5, 3, 4, 5, and 24 h from the start of docetaxel infusion. Blood samples were centrifuged at 3000 rpm for 15 min and supernatant plasma was collected and stored at −80°C until the time of analysis. Deviations from the protocol time occurred due to practical reasons, but the actual time of sampling was recorded and used for analysis. Plasma docetaxel was quantitated using an LC–MS method developed and validated at our laboratory, which has an intra- and inter-day precision of <7% and accuracy of 96–110%.[14] The LC–MS system consisted of an API 2000 triple quadrupole mass spectrometer (Applied Biosystems/MDS SCIEX, ON, Concord, Ontario, Canada) and an Agilent 1100 autosampler injector with 100-μL loop and 1100 column oven at 23°C (Agilent Technologies, Waldbronn, Germany). Chromatographic separations were carried out using an Eclipse XDB-C8 column (50 × 2.1 mm, inside diameter 5 μm; Agilent Technologies, USA). The mobile phase was HPLC-grade acetonitrile/0.1% formic acid aqueous solution (60:40) delivered at a flow rate of 0.2 mL/min.

The AUC was estimated using the trapezoidal rule with log-extension to infinity based on the last three points. The half-life ($t_{1/2}$) was calculated as $\ln 2/k$ and the elimination rate constant k was estimated as the negative of the slope from a linear regression of log concentration of time. Drug clearance (Cl) and the volume of distribution (Vd) were estimated as dose/AUC and Cl/k, respectively. Interindividual variability and intra-individual variability of docetaxel clearance, volume of distribution, and half-life were estimated with multilevel modeling for repeat measures in which the fixed effects and residual variance represents the inter- and intra-individual variance, respectively. We assumed IOV to approximate intra-indi-

vidual variability. An IOV parameter was included if it improved model fitting ($P < 0.10$ under the conservative likelihood ratio test against a linear model with only fixed effects). Interoccasion variability was approximated as the intra-individual variability. Both IIV and IOV were expressed as coefficients of variation (CV%) by taking the square roots of the estimates divided by the mean parameter value. Descriptive statistics were used to summarize PK parameters.

Skewed PK parameters were log-transformed, and PK parameters were compared between groups using one-way ANOVA. The overall *F*-test was used to assess whether any pair of groups had unequal variances, and this was followed by *post-hoc* multiple comparisons test if prompted, and corrected using Scheffé's method, which is robust against unequal sample sizes. Pharmacodynamic parameters involving neutrophil counts were compared between groups using the Kruskal–Wallis test followed by *post-hoc* Dunn's test if prompted. Non-compartmental PK analysis, mixed-effects multilevel modelling, and statistical tests were carried out in STATA/MP 13.0 (StataCorp, College Station, TX, USA).

Results

Patients. Thirty-three patients of Asian ethnicities were treated, of whom 23 were assigned to receive docetaxel 40 mg/m^2 (Category 1), six patients to 30 mg/m^2 (Category 2), and four patients to 20 mg/m^2 (Category 3). Patient demographics and clinical covariates at baseline are presented in Table 1. Median liver enzyme levels showed a positive association with liver dysfunction severity, while plasma protein levels showed a negative association. None of the patients received granulocyte-colony stimulating factor during the course of the study. In 23 patients for whom information on encephalopathy, ascites, and INR at baseline was available, we evaluated the Child–Pugh score by searching the patients' electronic medical records and case record file *post-hoc*.

Pharmacokinetics of docetaxel. Summary PK of docetaxel are listed in Table 2 and PK profiles are shown in Fig. 1. Two PK measurements (baseline and repeat) were available for 28 patients and five patients had PK sampling performed on only one occasion due to rapidly progressive disease ($n = 3$), clinical deterioration ($n = 1$), and death ($n = 1$), yielding 61 PK profiles for analysis. Three patients in Category 1 were switched to a standard 3-weekly dose regimen for cycle 2 due to inadvertent protocol deviation, and repeat PK for these three patients were only undertaken at the start of cycle 2. They were therefore excluded from exposure and safety analyses. Docetaxel clearance decreased with worsening liver dysfunction. Docetaxel clearance was significantly different between Category 1 and Category 2 (corrected $P = 0.022$) or Category 3 (corrected $P < 0.001$) and between Category 2 and Category 3 before adjustment (nominal $P = 0.0431$), which showed a trend after correction for multiple comparison (corrected $P = 0.096$). Median body surface area-adjusted docetaxel clearance was 22.8, 16.4, and 11.3 L/h/m^2 in patients with normal, mild, and moderate liver dysfunction, respectively. This represents a 28–50% reduction in patients with mild to moderate liver dysfunction compared with patients with normal liver function.

High interpatient and intrapatient variability in the PK of docetaxel was observed. However, interpatient variability of body surface area-adjusted docetaxel clearance was lower in mild (33.3%) and moderate (42.0%) liver dysfunction patients compared to normal liver function patients (46.3%). Interocca-

Table 1. Baseline characteristics of cancer patients with hepatic dysfunction

	Category 1 ($n = 23$)	Category 2 ($n = 6$)	Category 3 ($n = 4$)
Sex (male/female)	16/7	3/3	0/4
Age, years			
Median (range)	59.5 (35.0–76.0)	61.0 (36.0–73.0)	62.5 (41.0–65.0)
Mean ± SD	58.5 ± 10.9	57.3 ± 13.3	57.8 ± 11.2
Ethnicity			
Chinese	19	6	4
Malay	3	0	0
Indian	1	0	0
Performance status (ECOG)			
0	9	2	1
1	14	3	3
2	0	1	0
Child–Pugh score†			
Median (range)	5 (5–6)	5	6.50 (5–10)
Mean ± SD	5.07 ± 0.288	5	7.00 ± 1.64
No. of patients with CP 5/6/7/8/9/10	14/1/0/0/0/0	5/0/0/0/0/0	1/1/0/0/0/1
Tumor site (primary and metastases)			
Lung	13	1	0
Head and Neck	3	1	0
Bone	1	1	0
Prostate	2	0	0
Pancreas	0	1	0
Breast	5	3	3
Gastric	1	0	0
Gallbladder	0	0	1
Liver	1	0	0
No. of prior chemotherapy regimens			
0	1	0	0
1	1	0	1
2	17	5	1
>2	4	1	2
Baseline laboratory values (mean ± SD, median)			
Platelets, $\times 10^9$/L	315 ± 101, 278	263 ± 93.9, 240	283 ± 175, 276
ANC, $\times 10^9$/L	5.63 ± 3.43, 5.73	6.40 ± 2.66, 6.49	5.55 ± 4.31, 4.66
Creatinine, μmol/L	80.5 ± 20.7, 82	72.8 ± 21.1, 63	37.6 ± 28.7, 43
Protein, g/L	73.7 ± 5.95, 73	71.7 ± 8.62, 69	67 ± 4.24, 67
Albumin, g/L	41.8 ± 4.49, 42	38.7 ± 2.66, 38.5	31 ± 6.58, 31
Bilirubin, μmol/L	9.30 ± 3.90, 9	12 ± 7.10, 10.5	21.3± 12.7, 20.5
AST, U/L	24.4 ± 8.72, 23.5	103 ± 39.0, 103	267 ± 154, 262
ALP U/L	130 ± 196, 96	247 ± 147, 250	614 ± 677, 304

†International normalized ratio for Child–Pugh (CP) score computation was only available for 23 patients. Hepatic dysfunction categorized as: Category 1, normal; Category 2, mild – alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase ≤5× upper limit of normal (ULN), and total bilirubin within normal range; and Category 3, moderate – any alkaline phosphatase, and aspartate aminotransferase or alanine aminotransferase ≤5–10× ULN, and/or total bilirubin ≤1–1.5× ULN. ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group.

Table 2. Non-compartmental pharmacokinetic analysis of docetaxel in cancer patients with hepatic dysfunction

	Category 1		Category 2		Category 3		All patients	
	(n = 23)		(n = 6)		(n = 4)		(n = 33)	
	Mean (CV%)	Median (range)	Mean (CV%)	Median (range)	Mean (CV%)	Median (range)	Mean (CV%)	Median (range)
Docetaxel clearance (CL_{DTX}, L/h), *overall*	41.4 (41.8)	38.3 (9.61–105)	25.7 (29.4)	25.5 (14.0–44.3)	16.2 (41.0)	15.6 (4.98–26.1)	35.8 (50.7)	33.4 (4.98–105)
Baseline	43.4 (47.5)	36.7 (13.4–105)	27.9 (37.0)	26.7 (14.0–44.3)	15.5 (55.4)	15.6 (4.98–26.1)	37.2 (55.6)	31.4 (4.98–105)
Repeat	39.0 (43.0)	38.7 (9.61–78.1)	23.4 (35.9)	21.9 (14.4–34.5)	17.5 (28.0)	17.5 (14.0–20.9)	34.1 (48.7)	31.4 (9.61–78.1)
Docetaxel clearance/BSA, *overall* (CL_{DTX}, L/h/m^2)	25.3 (46.3)	22.8 (6.0–65.7)	16.6 (33.3)	16.4 (8.44–25.1)	11.7 (42.0)	11.3 (3.98–18.6)	22.3 (51.0)	21.2 (3.98–65.7)
Baseline	26.7 (48.5)	22.2 (8.36–65.7)	17.9 (32.6)	17.2 (8.96–25.1)	11.3 (52.8)	11.3 (3.98–18.6)	23.1 (55.0)	20.1 (3.98–65.7)
Repeat	23.8 (43.3)	19.5 (6.01–45.5)	15.2 (35.1)	15.4 (8.44–22.3)	12.5 (28.0)	12.5 (10.0–15.0)	21.1 (47.1)	19.5 (6.01–45.5)
Interoccasion variability on CL_{DTX} (IOV_{CL}, %)	21.9 (16.6)	–	18.3 (28.9)	–	18.4 (50.4)	–	22.5 (13.8)	–
Volume of distribution at steady-state (Vd_{ss}, L)	299 (36.4)	255 (69–1292)	212 (23.9)	183 (101–458)	148 (32.7)	145 (42.8–219)	269 (40.5)	219 (42.8–1292)
Interoccasion variability on V_d (IOV_{Vd}, %)	71.7 (37.7)	–	39.3 (28.9)	–	33.3 (28.9)	–	69.5 (15.4)	–
Half-life ($t_{1/2}$; h)	13.9 (9.03)	12.6 (6.31–50.5)	14.7 (11.1)	13.5 (10.1–21.6)	14.3 (2.83)	13.2 (10.4–19.8)	14.1 (8.04)	13.2 (6.31–50.5)
Interoccasion variability on $t_{1/2}$ ($IOV_{t1/2}$, %)	47.4 (10.8)	–	16.0 (28.9)	–	23.2 (28.9)	–	41.0 (9.05)	–

Hepatic dysfunction categorized as: Category 1, normal; Category 2, mild – alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase ≤5× upper limit of normal (ULN), and total bilirubin within normal range; and Category 3, moderate – any alkaline phosphatase, and aspartate aminotransferase or alanine aminotransferase ≤5–10× ULN, and/or total bilirubin ≤1–1.5× ULN. –, not applicable.

sion variability of docetaxel clearance was relatively less (22.5%) compared to the interindividual variability. The apparent volume of distribution of docetaxel decreased with worsening liver function, and ranged from 48.2 to 1292 L for all patients. Interoccasion variability (69.5%) in the volume of distribution for all patients was a greater component of variance compared to IIV (40.5%). The median serum docetaxel half-life was relatively similar between groups and ranged from 12.6 to 13.5 and 13.2 h for normal liver function, mild, and moderate liver dysfunction patients, respectively. Of 28 patients with evaluable AUC performed on repeat PK, 4 received dosages that were reduced by 25% compared to baseline dosage, and this should be taken into account when interpreting the AUC of the second observation. Docetaxel AUC was lognormally distributed and the median AUC of all observations were 1.74, 1.83, and 1.77 mg·h/L in Categories 1, 2, and 3, respectively (Table 3). Exposure was not significantly different between groups at baseline PK (P = 0.55), repeat PK (P = 0.77), or when PK samples were combined (P = 0.52).

Safety and tolerability assessment. The occurrence of severe treatment-related adverse events are listed in Table 4. Among the 30 evaluable patients, the most common toxicity attributed to weekly docetaxel was myelosuppression, in particular neutropenia (30%), which led to dose modifications in 9 patients. Severe anemia, fatigue, hypersensitivity, mucositis, sepsis, thrombocytopenia, and diarrhea were less frequent.

Docetaxel exposure (P = 0.332) and clearance (P = 0.627) at baseline were not significantly different between patients who required dose modifications and those who did not. Neutropenia between groups was also assessed (Fig. 2). The median lowest ANC was 1.40, 1.61, and 1.22 × 10^9/L for Category 1, 2, and 3 patients, respectively, and was not significantly different between any pair of groups (P = 0.960). The relative decrease in neutrophil count between baseline and nadir was also assessed, and this was −67.7%, −78.0%, and −60.2% in Category 1, 2, and 3 patients, respectively, and no significant differences were detected between any pair of groups (P = 0.707).

Proposed classification versus Child–Pugh and NCI-ODWG grouping systems. The classification system for hepatic dysfunction severity in the present study uses AST, ALT, ALP, and TB. These selected covariates were identified on the basis of their significant correlation specifically with docetaxel PK. Patients were separated into three groups, comprising 23 (Category 1), 6 (Category 2), and 4 (Category 3) patients. An unplanned analysis was carried out to compare the current grouping system with that of the Child–Pugh and NCI-ODWG systems on a retrospective basis. As baseline INR values were not collected prospectively, only 23 (Category 1, n = 15 [65%]; Category 2, n = 5 [83%]; Category 3, n = 3 [75%]) patients were evaluable for Child–Pugh score computation. As is evident, missing data does not appear to be random, as a smaller fraction of patients classified as having normal hepatic status had INR taken, whereas patients with mild or moderate hepatic dysfunction were more likely to have baseline INR. On a retrospective basis, 22 of 23 patients would be categorized as Child–Pugh Group A and 1 patient would be categorized as Child–Pugh Group C. The average Child–Pugh scores were 5.07 ± 0.29, 5.00 ± 0.00, and 7.00 ± 1.64 in patients which we categorized as having normal, mild, and moderate

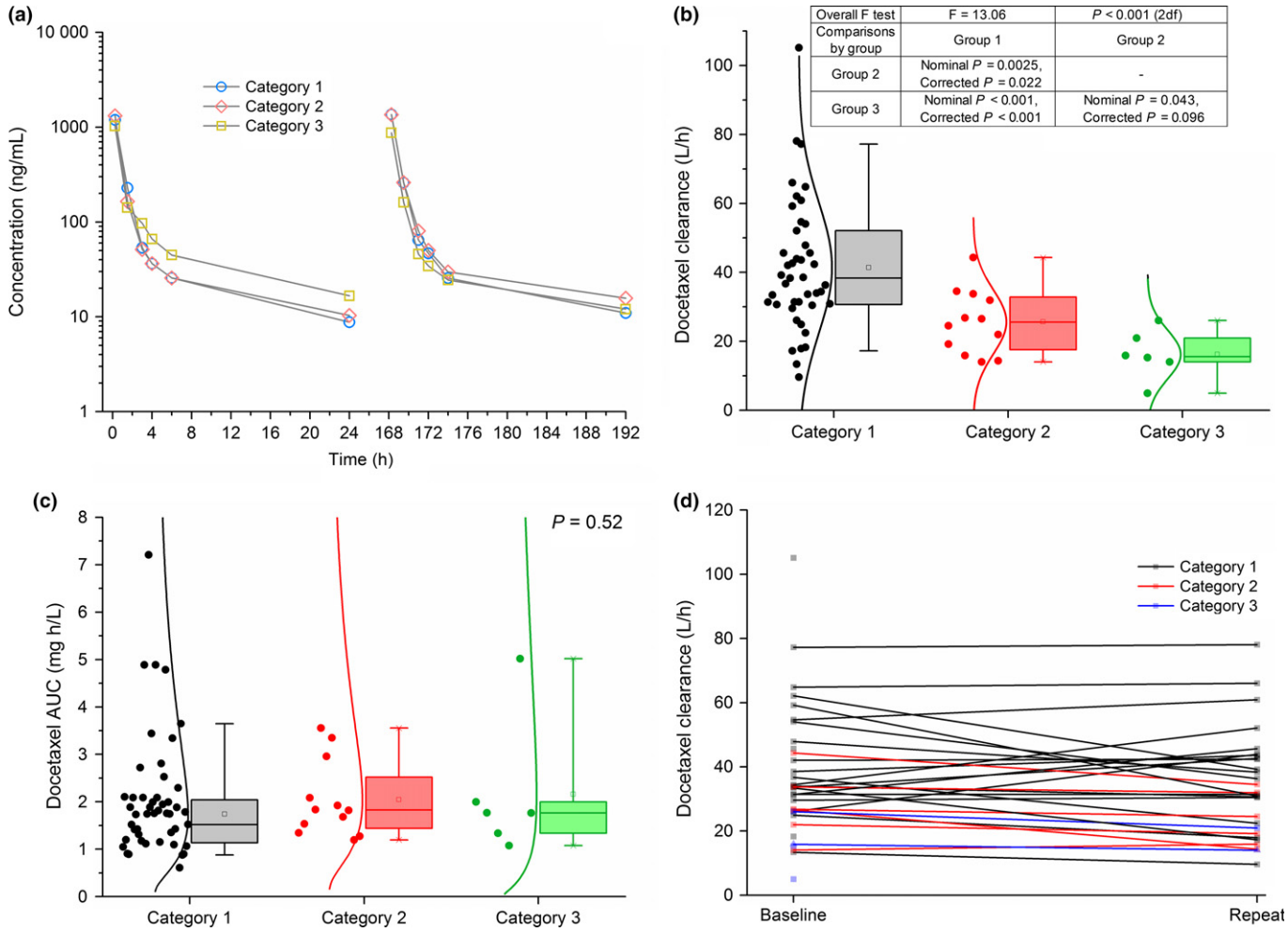

Fig. 1. Non-compartmental pharmacokinetics of docetaxel in cancer patients categorized according to hepatic dysfunction: Category 1, normal; Category 2, mild – alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase ≤5× upper limit of normal (ULN), and total bilirubin within normal range; and Category 3, moderate – any alkaline phosphatase, and aspartate aminotransferase or alanine aminotransferase ≤5–10× ULN, and/or total bilirubin ≤1–1.5× ULN. (a) Mean docetaxel concentrations. (b) Docetaxel clearance. (c) Docetaxel exposure. (d) Changes in docetaxel clearance between baseline and repeat pharmacokinetic measurement. AUC, area under the concentration–time curve.

dysfunction, respectively (Table 1). We also evaluated the NCI-ODWG classification: the cut-off TB level used to differentiate NCI-ODWG normal and NCI-ODWG mild patients is the 1× ULN. On this basis, 29 of 33 patients in our study would be categorized into NCI-ODWG normal hepatic function group, and 4 other patients would be deemed as having mild hepatic dysfunction according to NCI-ODWG.

Discussion

We carried out the first prospective study to evaluate the utility of a dosing nomogram towards therapeutic drug monitoring in patients with hepatic dysfunction. The translational aspect is in the use of liver function biomarkers for classification of hepatic status and dose modification. The aim of the study was to provide greater guidance for clinical oncologists who have to treat this subpopulation.

In this study, the dose reductions specified in the nomogram were −25% and −50% for patients with elevated transaminases, ALP, and TB as specified above. Clinically, the dosing modifications are in noteworthy agreement with Minami and colleagues' recommendations in an earlier issue in this journal,[6] which are approximately −20% and −40% reductions in the starting dose for patients with grade 2 (>3.0–5.0× ULN) and grade 3 (>5.0–20.0× ULN) elevations of transaminases. We acknowledge that in patients with liver metastasis, liver function may vary drastically in severe cases. Only one patient presented with a liver metastasis in our study, and in fact had normal liver function (Category 1) at baseline. In the present study, hematology and chemistries were carried out within a clinically practicable 1-week timeframe prior to treatment; however, baseline evaluations should be undertaken closer to the start of treatment in patients with liver metastasis.

The data reported here show that docetaxel clearance is reduced in patients with liver dysfunction. We found median bodyweight-normalized docetaxel clearance to be reduced by 28–50% in Category 2 and Category 3 liver dysfunction patients compared with Category 1 patients, suggesting that there may be sound rationale for adjusting the starting dosages to 40, 30, or 20 mg/m^2 for Category 1, 2, and 3 patients, respectively. This reduction in drug elimination is also higher than a previous observational report that found docetaxel clearance to be reduced by 12–27% in patients with elevated bilirubin and/or transaminases.[5] The median $AUC_{0-\infty}$ in all three

Table 3. Docetaxel $AUC_{0-\infty}$ (mg·h/L) in cancer patients with hepatic dysfunction

	Category 1	Category 2	Category 3	*P*-value
Baseline				0.707
No. of observations	23	6	4	–
Median	1.755	1.749	1.765	–
Repeat†				0.539
No. of observations	17	6	2	–
Of which dosage was reduced by 25%	4	0	0	–
Median	1.522	1.96	1.667	–
Overall†				0.524
No. of observations	40	12	6	–
Median	1.738	1.827	1.765	–
Geometric mean (95% confidence)	1.65 (1.43–1.90)	1.92 (1.52–2.42)	1.89 (1.08–3.29)	–

†Three patients from Category 1 were switched to the 3-weekly cycle when the repeat pharmacokinetic analyses were carried out, and were thus excluded from area under the concentration–time curve (AUC) calculations. Hepatic dysfunction categorized as: Category 1, normal; Category 2, mild – alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase ≤5× upper limit of normal (ULN), and total bilirubin within normal range; and Category 3, moderate – any alkaline phosphatase, and aspartate aminotransferase or alanine aminotransferase ≤5–10× ULN, and/or total bilirubin ≤1–1.5× ULN.

Table 4. Maximum non-hematologic and hematologic treatment-related grade 3/4 adverse events in cancer patients with hepatic dysfunction treated with docetaxel

Grade 3/4 toxicities	Category 1 (%) *n* = 20†	Category 2 (%) *n* = 6	Category 3 (%) *n* = 4
Anemia	0 (0)	0 (0.0)	1 (25)
Fatigue	0 (0)	1 (16.7)	0 (0)
Hypersensitivity	1 (5)	0 (0.0)	0 (0)
Mucositis	0 (0)	1 (16.7)	0 (0)
Neutropenia	6 (30)	2 (33.3)	1 (25)
Sepsis	0 (0)	0 (0.0)	1 (25)
Thrombocytopenia	0 (0)	0 (0.0)	1 (25)
Diarrhea	1 (5)	0 (0.0)	0 (0)
Required dose modification	6 (30)	2 (33.3)	1 (25)

†Three patients with normal liver function were excluded from safety analysis as they received a 3-weekly dosage in cycle 2. Hepatic dysfunction categorized as: Category 1, normal; Category 2, mild – alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase ≤5× upper limit of normal (ULN), and total bilirubin within normal range; and Category 3, moderate – any alkaline phosphatase, and aspartate aminotransferase or alanine aminotransferase ≤5–10× ULN, and/or total bilirubin ≤1–1.5× ULN.

strata of patients ranged from 1.738 to 1.827 mg·h/L (Table 3), indicating that this is a safe and acceptable range for therapeutic drug monitoring in patients treated on a weekly docetaxel schedule. Interestingly, IIV in docetaxel clearance was lower in liver dysfunction patients compared to normal liver function patients. This might be explained by docetaxel being extensively metabolized by polymorphic hepatic CYP3A,[3] and hepatic dysfunction abrogating the contribution of CYP3A polymorphisms to interindividual variability.

However, this study has its limitations. The fraction of protein-unbound docetaxel and AAG levels are potentially relevant factors that may add further clarification on exposure–toxicity relationships. For example, the PK exposure parameters of unbound concentration of docetaxel was shown to be predictive of neutropenia,[15] and the associations between AAG levels and docetaxel PK, toxicity, and efficacy have been reported previously.[11,16] However, these two parameters were not measured in the present study because AAG levels and unbound docetaxel concentrations are not routinely ordered clinically, and it was also not an aim of the study to perform predictive PK or to examine the relationship of predictive covariates with drug toxicity.

The regimen here uses a weekly docetaxel schedule, which is of growing clinical relevance and interest because of its reported improved tolerability. Several meta-analyses have found the weekly infusion schedule to be associated with lower toxicity.[17,18] In the case of liver dysfunction patients, we contend that a weekly docetaxel schedule further offers the benefit of minimising the risk of accidental over-dosing due to uncertainty in the dosing requirements of liver dysfunction patients. Overall, this dosing regimen appears to be well-tolerated in all three categories of patients at the given dosages. Pharmacokinetic variability and pharmacodynamic variability were reduced as a result of risk-stratified dosing. Neutropenia (nadir ANC and the maximum decrease in neutrophil counts between baseline and nadir) were not significantly different between patient categories, likely because variability in docetaxel exposure was reduced.

An unplanned analysis to compare the discriminatory power of Child–Pugh and NCI-ODWG indices compared to the proposed classification was also carried out. We found that patients with differential docetaxel clearance and dose requirements were grouped in a more distributed manner using the proposed classification system. However, the results of the comparison with the Child–Pugh system should be taken with caution as only 23 of 33 patients were evaluable for Child–Pugh scores. As patients with more severe liver dysfunction were more likely to have baseline INR readings, the effect of missing INR could introduce bias into the comparison. In this retrospective assessment, 22 of 23 patients were classified as Child–Pugh Group A and 1 as Child–Pugh Group B, whereas 29 of 33 patients were classified as NCI-ODWG normal and 4 as NCI-ODWG mild. The apparent inadequacy in discriminatory power of the two established classification systems could be due to the weights they assign to different criterion (such as

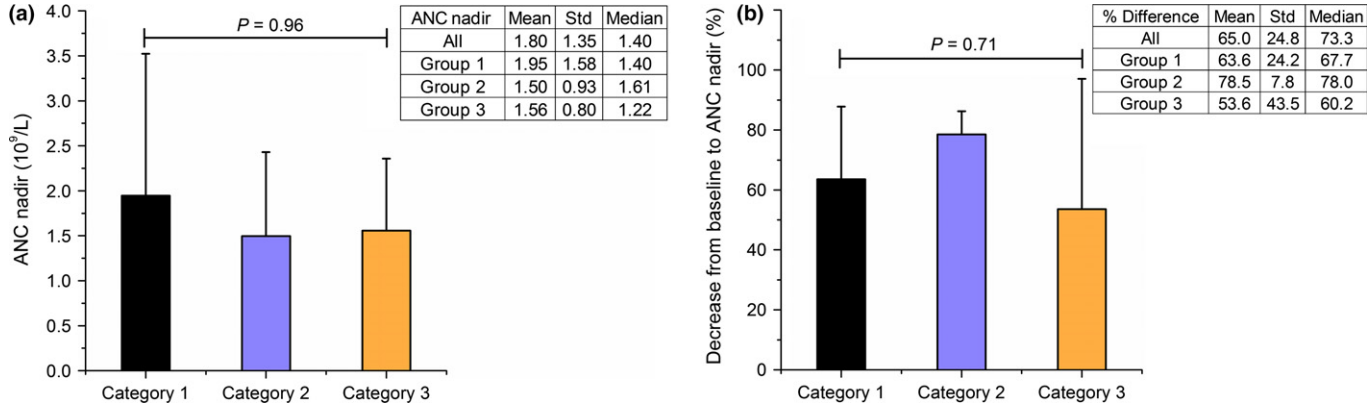

Fig. 2. Pharmacodynamics of docetaxel-induced neutropenia. (a) Mean ± SD of nadir absolute neutrophil count (ANC). (b) Mean ± SD of the maximum decrease between ANC at baseline compared to nadir. Three patients from Category 1 were switched to the 3-weekly cycle when the repeat pharmacokinetic assessment was carried out, and were thus excluded from pharmacodynamic analysis. Hepatic dysfunction categories were defined as: Category 1, normal; Category 2, mild – alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase ≤5× upper limit of normal (ULN), and total bilirubin within normal range; and Category 3, moderate – any alkaline phosphatase, and aspartate aminotransferase or alanine aminotransferase ≤5–10× ULN, and/or total bilirubin ≤1–1.5× ULN. Std, standard.

ascites, encephalopathy, and INR in Child–Pugh, and a high cut-off TB level in NCI-ODWG) which are not specific to docetaxel regimens. In fact, it is likely that the extent of the effect of hepatic dysfunction on drug disposition varies depending on the chemotherapeutic agent in question, as various drugs are metabolized and excreted through different pathways. It is therefore plausible that more sensitive and appropriate organ dysfunction classification criteria should be developed that are specific to individual chemotherapeutic agents.

To conclude, our results provide evidence of altered docetaxel PK in the presence of liver dysfunction. We offer a new, sensitive, and clinically practicable classification criteria that more effectively segregates patients with differential dose requirements compared to the NCI-ODWG and Child–Pugh systems, and the docetaxel dosages coupled to this alternative classification system appear to be safe and tolerable. This prospective, translational study goes towards providing guidance for safer chemotherapy use, and should motivate external validation studies.

Acknowledgments

The study was carried out at the National University Cancer Institute, Singapore. This work was supported by the National Medical Research Council (NMRC/TCR/009-NUHS/2013 to W.P.Y., NMRC/CSA/021/2010 to B.C.G).

Disclosure Statement

The authors have no conflict of interest.

Abbreviations

AAG	alpha-1-acid glycoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
CYP	cytochrome P450
IIV	interindividual variability
INR	international normalized ratio
IOV	inter-occasion variability
LC–MS	liquid chromatography–mass spectrometry
NCI-ODWG	National Cancer Institute-Organ Dysfunction Working Group
PK	pharmacokinetics
TB	total bilirubin
ULN	upper limit of normal

References

1 Edwards BK, Noone AM, Mariotto AB *et al.* Annual Report to the Nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer* 2014; **120**: 1290–314.
2 Field KM, Michael M. Part II: Liver function in oncology: towards safer chemotherapy use. *Lancet Oncol* 2008 Dec; **9**: 1181–90.
3 Tran A, Jullien V, Alexandre J *et al.* Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. *Clin Pharmacol Ther* 2006 Jun; **79**: 570–80.
4 Field KM, Dow C, Michael M. Part I: Liver function in oncology: biochemistry and beyond. *Lancet Oncol* 2008 Nov; **9**: 1092–101.
5 Clarke SJ, Rivory LP. Clinical pharmacokinetics of docetaxel. *Clin Pharmacokinet* 1999 Feb; **36** (2) : 99–114.
6 Minami H, Kawada K, Sasaki Y *et al.* Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice. *Cancer Sci* 2009; **100** (1) : 144–9.
7 Bruno R, Hille D, Riva A *et al.* Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. *J Clin Oncol* 1998 Jan; **16** (1) : 187–96.
8 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973 Aug; **60**: 646–9.
9 Patel H, Egorin MJ, Remick SC *et al.* Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): Implications for chemotherapy dosing. *ASCO Meet Abstr* 2004 Jul; **22** (Suppl): 6051.
10 Millward MJ, Boyer MJ, Lehnert M *et al.* Docetaxel and carboplatin is an active regimen in advanced non-small-cell lung cancer: a phase II study in Caucasian and Asian patients. *Ann Oncol* 2003 Mar; **14**: 449–54.
11 Kenmotsu H, Tanigawara Y. Pharmacokinetics, dynamics and toxicity of docetaxel: why the Japanese dose differs from the Western dose. *Cancer Sci* 2015 May; **106**: 497–504.
12 Goh BC, Lee SC, Wang LZ *et al.* Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians

through phenotyping and genotyping strategies. *J Clin Oncol* 2002; **20**: 3683–90.
13 D'Argenio D, Schumitzky A. ADAPT II User's Guide: Pharmacokinetic/pharmacodynamic systems analysis software. Biomed Simulations Resour Los Angeles; 1997.
14 Wang LZ, Goh BC, Grigg ME, Lee SC, Khoo YM, Lee HS. A rapid and sensitive liquid chromatography/tandem mass spectrometry method for determination of docetaxel in human plasma. *Rapid Commun Mass Spectrom* 2003 Jan; **17**: 1548–52.
15 Minami H, Kawada K, Sasaki Y *et al.* Pharmacokinetics and pharmacodynamics of protein-unbound docetaxel in cancer patients. *Cancer Sci* 2006; **97**: 235–41.
16 Loos WJ, Baker SD, Verweij J, Boonstra JG, Sparreboom A. Clinical pharmacokinetics of unbound docetaxel: role of polysorbate 80 and serum proteins. *Clin Pharmacol Ther* 2003 Oct; **74**: 364–71.
17 Mauri D, Kamposioras K, Tsali L *et al.* Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer Treat Rev* 2010 Feb; **36**: 69–74.
18 Di Maio M, Perrone F, Chiodini P *et al.* Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2007 Apr; **25**: 1377–82.