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SHORT COMMUNICATION

The effects of *CYP3A4*, *CYP3A5*, *ABCB1*, *ABCC2*, *ABCG2* and *SLCO1B3* single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of docetaxel in nasopharyngeal carcinoma patients

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Abstract
Purpose This exploratory study aimed to explain the interindividual variabilities of docetaxel pharmacokinetics and pharmacodynamics in Asian nasopharyngeal carcinoma patients ($n = 54$) through the genotyping of *CYP3A4*, *CYP3A5*, *ABCB1*, *ABCC2*, *ABCG2* and *SLCO1B3* genes.
Methods Docetaxel was administered over 1 h on days 1, 8, and 15 every 28 days at 30 mg/m^2/dose. Genomic DNA was isolated from peripheral blood and genotyped for the selected polymorphisms in the candidate genes. Docetaxel pharmacokinetic parameters were estimated by non-compartmental modelling.
Results Patients homozygous for the variant allele (GG) of *SLCO1B3* rs11045585 (IVS12-5676A > G) had significantly higher area under the plasma concentration–time curve of docetaxel ($P = 0.026$) and lower clearance ($P = 0.036$) compared to patients with AA/AG genotypes. Patients harbouring the heterozygous genotype (GA + GT + TA) for *ABCB1* rs2032582 (2677G > T/A) had the highest percentage decrease in nadir haemoglobin from cycle 1 baseline compared to those with GG/TT genotypes ($P = 0.006$). Similar trend was observed for *ABCB1* rs1045642 (3435C > T) with heterozygotes (CT) having the highest percentage decrease in nadir haemoglobin from cycle 1 baseline compared to those with CC/TT genotypes ($P = 0.066$).
Conclusions This study suggests that the cooperative influence of functional polymorphisms in *SLCO1B3* and *ABCB1* genes may be responsible for the interindividual variability in docetaxel disposition in Asian nasopharyngeal cancer patients.

Keywords Asians · Docetaxel · Nasopharyngeal cancer · Pharmacogenetics · Polymorphisms

Abbreviations

SNP	Single nucleotide polymorphism
NPC	Nasopharyngeal cancer
C_{max}	Peak plasma concentration
AUC_{0-inf}	Area under plasma concentration–time curve from time zero to infinity
CL	Plasma clearance

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Introduction

Docetaxel belongs to the taxane class of anti-mitotic chemotherapeutic agents and is frequently used in the treatment of a wide variety of solid tumours. The pharmacokinetics of docetaxel exhibits wide interindividual variability that may lead to poor predictability of treatment-related side effects and outcomes. Therefore, it is of clinical importance to identify the sources of interindividual variability in specific

patient population groups in order to optimise the drug therapy.

The disposition of docetaxel is mainly mediated by CYP3A4 and CYP3A5 enzymes and transporters such as ABCB1, ABCC2 and SLCO1B3 [1]. The role of another efflux transporter, ABCG2 (breast cancer resistance protein) in docetaxel disposition, however, is controversial. Several studies have shown that the candidate genes encoding these proteins are polymorphic and their genetic variations were associated with functional effects in either in vitro *or* in vivo model systems [2–10]. Hence, it can be postulated that genetic variations present in these genes may affect the disposition of docetaxel, consequently altering the drug's pharmacokinetic and pharmacodynamic characteristics. Previous studies have revealed mixed findings regarding the influence of functional polymorphisms in these genes in affecting docetaxel dispositions [1]. Furthermore, as most previous studies were performed in Caucasians, there is a need to study Asian populations because the genetic variations in the respective candidate genes are known to exhibit wide interethnic differences amongst different ethnic groups [11].

The objective of this exploratory study was thus to comprehensively investigate the pharmacogenetics of drug metabolism enzymes (CYP3A4, CYP3A5) and drug transporters (ABCB1, ABCC2, ABCG2, SLCO1B3) across the docetaxel disposition pathway and their influence on docetaxel disposition in sixty Asian nasopharyngeal cancer (NPC) patients. The clinical phase II component ($n = 30$) of the study was previously reported elsewhere [12].

Methods

Subjects

A total of 60 NPC patients were recruited in this study. The design of the clinical phase II study was described previously [12]. All participants provided written informed consent, and the study was approved by the ethics review committee of National Cancer Centre, Singapore.

Docetaxel treatment and pharmacokinetics in NPC patients

Docetaxel (Taxotere; Sanofi-Aventis, Paris, France) was administered over 1 h on days 1, 8, and 15 every 28 days at 30 mg/m^2/dose. Blood samples were collected at predose (0 h), 0.5 h and 1 h (end of infusion), then at 15 min, 30 min, 2 h, 4 h, 7 h and 23 h after the end of docetaxel infusion in the first cycle. Docetaxel plasma concentrations were determined with slight modifications of a validated HPLC method [13]. A mixture of acetonitrile-*n*-butylchloride (1:4, v/v) was added to 200 µl of human plasma. Separation was accomplished on Spherisorb ODS2 column (5 µm, 250 × 4.6 mm; Waters, MA, USA). Non-compartmental pharmacokinetics modelling was performed by WinNonLin version 2.1 (Pharsight, CA, USA).

Pharmacodynamic parameters

The percentage decrease in absolute neutrophil count, platelet count and haemoglobin count was defined as:

$$(\text{Pre-treatment value} - \text{Nadir value})/\text{Pre-treatment value} \times 100$$

where the pre-treatment value corresponded to the baseline value and nadir value denoted the lowest value measured in cycle 1. Toxicity evaluations were described in previous publication [12].

Pharmacogenetic analysis

Genomic DNA of all patients was isolated from blood by using Puregene DNA isolation kit (Qiagen, CA, USA). The SNPs in *CYP3A4*, *CYP3A5*, *ABCB1*, *ABCC2*, *ABCG2* and *SLCO1B3* were analysed based on anticipated functional effects as reported in previous studies [2, 4, 5, 7, 11, 14]. The SNPs examined were as follows—*CYP3A4*: *CYP3A4*1B* (rs2740574), IVS6-191C > T (rs35599367); *CYP3A5*: *CYP3A5*3* (rs776746), *CYP3A5*6* (rs10264272); *ABCB1*: 1236C > T (rs1128503), 2677G > T/A (rs2032582), 3435C > T (rs1045642); *ABCC2*: *+9383C > G (rs12762549); *ABCG2*: 421C > A (rs2231142); *SLCO1B3*: 334T > G (rs4149117), 439A > G (rs57585902), 699G > A (rs7311358), 767G > C (rs60140950), 1559A > C, 1564G > T (rs72559743), 1679T > C (rs12299012) and IVS12-5676A > G (rs11045585). As *SLCO1B3* SNPs, *CYP3A4* rs35599367 and *ABCC2* rs12762549 have not been previously investigated in healthy Asian subjects, a total of 168 healthy subjects (Chinese, Malay, Indian, $n = 56$ per ethnic group) were screened for the examined genetic variants prior to genotyping in the patient population. All SNPs were analysed by direct sequencing using Applied Biosystems 3730 DNA Analyser (Applied Biosystems Inc, CA, USA).

Statistical analysis

The Fisher's exact test was used to determine conformity with Hardy–Weinberg equilibrium. The Kruskal–Wallis, Mann–Whitney *U* and Fisher's exact tests were used as appropriate to assess the differences in pharmacokinetics and pharmacodynamics parameters amongst different genotype groups. Spearman's rank correlation was adopted

to assess the correlation between pharmacokinetics parameters and patients' characteristics. The values of pharmacokinetic parameters are reported as median (range). The level of significance was set at $P < 0.05$ for all comparisons. All tests were conducted using SAS Version 9.2 (SAS Institute Inc., NC, USA).

Results

NPC patient demographics and clinical characteristics ($n = 54$)

A total of 54 patients completed the study. The mean age of the patients was 52.4 ± 7.8 years. Most of the patients were men (92.6%) compared with women (7.4%). The majority of the patients belonged to the Chinese ethnic group (92.6%), whilst Malay patients made up the remaining 7.4%.

Docetaxel pharmacokinetics in NPC patients

Pharmacokinetic measurement was taken in 59 patients. One patient did not have detectable level of docetaxel in the blood sample, and five were classified as outliers after repeated confirmation by HPLC. They were excluded from further analysis, thereby leaving a total of 54 assessable patients. The peak plasma concentration (C_{max}) and area under plasma concentration–time curve from time zero to infinity (AUC_{0-inf}) of these outliers were up to 38- and 32-fold higher than the median values of the rest of the patients, respectively, whilst the plasma clearance (CL) of these patients was up to 31-fold lower.

A wide degree of interindividual variability was inherent in the pharmacokinetic parameters with more than 6-, 8-, 9- and 13-fold variations observed for C_{max} [1.0 (0.5–3.1) μg/ml], AUC_{0-inf} [1.0 (0.6–4.7) h μg/ml], CL 46.4 (12.1–102.2) l/h] and volume of distribution [213.8 (53.4–713.3) l], respectively. Correlation analysis showed baseline albumin levels to be significantly correlated with AUC_{0-inf} and CL of docetaxel ($P = 0.006$ and $P = 0.003$, respectively). Other covariates such as age, body surface area, stage of tumour, weight, aspartate transaminase, alanine transaminase and total bilirubin were found not to significantly influence the pharmacokinetics of docetaxel.

Docetaxel pharmacokinetics–pharmacodynamics in NPC patients

Sixteen patients experienced grade 3 or 4 toxicities, including haematological and/or non-haematological toxicities. These patients displayed approximately 20% higher C_{max} [1.2 (0.6–2.7) vs. 1.0 (0.5–3.1) μg/ml, $P = 0.088$], 24% higher AUC_{0-inf} [1.2 (0.6–2.1) vs. 1.0 (0.6–4.7) h μg/ml, $P = 0.028$] and 17% lower CL [41.6 (22.0–98.6) vs. 49.8 (12.1–102.2) l/h, $P = 0.060$] compared with patients with grade 0–2 toxicities ($n = 38$) (Fig. 1a, b).

Frequency distributions and genotypic–phenotypic correlations of pharmacokinetic and pharmacodynamic parameters

Table 1 depicts the allele frequencies of the investigated SNPs in healthy Asian populations and NPC patients. Allelic frequencies of Asians and Caucasians from previously published reports are also included for comparison. The *SLCO1B3* rs4149117 and rs7311358 polymorphisms were in complete linkage disequilibrium ($R^2 = 1$, $|D'| = 1$) in the healthy Chinese population, and as such, all further analyses with regards to these polymorphisms were represented by rs7311358.

Table 2 shows the results of the influence of investigated polymorphisms in the various candidate genes on docetaxel pharmacokinetics. Patients harbouring the heterozygous genotype (GA + GT + TA) for *ABCB1* rs2032582 ($n = 32$) had the highest percentage decrease in

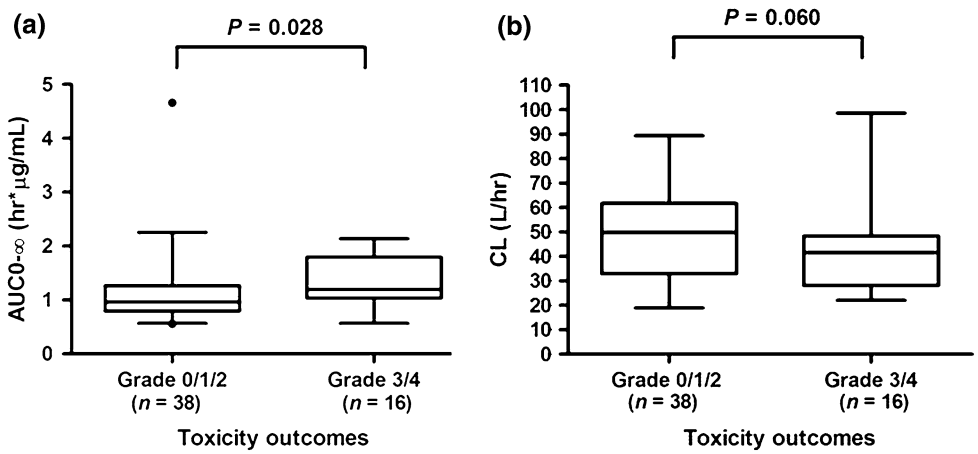

Fig. 1 The relationship between docetaxel **a** AUC_{0-inf}, **b** CL and overall toxicity outcomes. AUC_{0-inf}, area under plasma concentration–time curve from time zero to infinity; *CL* plasma clearance (Whiskers: 5–95 percentile)

Table 1 Allele frequencies of *CYP3A4*, *CYP3A5*, *ABCC2*, *ABCG2* and *SLCO1B3* in healthy Asian populations, NPC patients and comparisons with Caucasians

SNPs	rs ID	Allele	Allelic frequencies				
			Chinese	Malays	Indians	Caucasians	NPC patients
CYP3A4	(UCSC accession number NM_017460)						
*CYP3A4*1B*	rs2740574	A	1	1	1	0.98	1
		G	0	0	0	0.02	0
IVS6-191C > T	rs35599367	C	1	1	1	0.95 [2]	1
		T	0	0	0	0.05	0
CYP3A5	(Ensembl gene ID ENSG00000106258)						
*CYP3A5*3*	rs776746	A	0.24	0.39	0.41	0.15 [7]	0.33
		G	0.76	0.61	0.59	0.85	0.67
*CYP3A5*6*	rs10264272	G	1	1	1	1 [7]	1
		A	0	0	0	0	0
ABCB1	(UCSC accession number NM_000927)						
1236C > T	rs1128503	C	0.28	0.34	0.33	0.59 [15]	0.36
		T	0.72	0.66	0.67	0.41	0.64
2677G > A/T	rs2032582	G	0.38	0.53	0.33	0.56 [15]	0.51
(Ala893Ser/Thr)		A	0.12	0.03	0.07	0.02	0.10
		T	0.5	0.44	0.6	0.42	0.39
3435C > T	rs1045642	C	0.47	0.49	0.63	0.46 [15]	0.66
		T	0.53	0.51	0.37	0.54	0.34
ABCC2	(UCSC accession number NM_000392)						
*+9383C > G	rs12762549	C	0.4	0.4	0.55	NA	0.40
		G	0.6	0.6	0.45	NA	0.60
ABCG2	(UCSC accession number NM_004827)						
421C > A	rs2231142	C	0.72 [25]	0.73 [25]	0.85 [25]	0.88 [16]	0.71
(Gly141Lys)		A	0.28	0.27	0.15	0.12	0.29
SLCO1B3	(UCSC accession number NM_019844)						
334T > G	rs4149117	T	0.35	0.2	0.08	0.15 [14]	
(Ser112Ala)		G	0.65	0.8	0.92	0.86	
439A > G	rs57585902	A	1	1	1	0.995 [14]	1
(Thr147Ala)		G	0	0	0	0.005	0
699G > A	rs7311358	G	0.36	0.19	0.1	0.16 [14]	0.24
(Met233Ile)		A	0.64	0.81	0.9	0.84	0.76
767G > C	rs60140950	G	1	0.96	0.95	0.81 [14]	1
(Gly256Ala)		C	0	0.04	0.05	0.19	0
1559A > C	NA	A	1	1	1	1 [14]	1
(His520Pro)		C	0	0	0	0	0
1564G > T	rs72559743	G	1	1	1	0.98 [5]	1
(Gly522Cys)		T	0	0	0	0.02	0
1679T > C	rs12299012	T	1	1	1	0.98 [14]	1
(Val560Ala)		C	0	0	0	0.02	0
IVS12-5676A > G	rs11045585	A	0.82	0.82	0.97	NA	0.78
		G	0.18	0.18	0.03	NA	0.22

NA not available

The genotype and allele frequencies of *CYP3A4*1B*, *CYP3A5*3*, *ABCB1* 1236C > T, 2677G > T/A, 3435C > T in healthy Asian subjects are available in the previous publication [11]

Table 2 Summary of *SLCO1B3*, *ABCB1*, *ABCC2*, *ABCG2* and *CYP3A5* polymorphisms and their relationships with pharmacokinetics of docetaxel in Asian nasopharyngeal cancer patients ($n = 54$)

Pharmacokinetic parameters	Genotypes[a]			Overall *P* value	Pairwise *P* value
SLCO1B3					
699G > A	GG ($n = 1$)	GA ($n = 22$)	AA ($n = 29$)	GG versus GA versus AA	
C_{max} (μg/ml)	0.70 (0.70–0.70)	0.96 (0.58–2.00)	1.12 (0.51–3.08)	0.203	
AUC_{0-inf} (h μg/ml)	0.70 (0.70–0.70)	0.96 (0.60–4.66)	1.17 (0.56–2.14)	0.217	
CL (l/h)	55.96 (55.96–55.96)	47.92 (12.11–72.00)	43.60 (19.28–102.17)	0.526	
IVS12-5676A > G	AA ($n = 34$)	AG ($n = 16$)	GG ($n = 4$)	AA versus AG versus GG	AA + AG versus GG
C_{max} (μg/ml)	1.05 (0.58–3.08)	0.94 (0.51–1.63)	1.28 (0.96–2.00)	0.154	
AUC_{0-inf} (h μg/ml)	1.00 (0.57–4.66)	0.99 (0.56–1.97)	1.61 (1.27–2.08)	0.048	0.026
CL (L/hr)	46.73 (12.11–85.18)	51.48 (23.72–102.17)	29.63 (25.36–37.96)	0.049	0.036
ABCB1					
1236C > T	CC ($n = 8$)	CT ($n = 23$)	TT ($n = 23$)	CC versus CT versus TT	
C_{max} (μg/ml)	1.13 (0.58–3.08)	1.09 (0.51–2.00)	0.96 (0.55–2.66)	0.375	
AUC_{0-inf} (h μg/ml)	1.02 (0.57–2.13)	1.11 (0.56–2.06)	1.01 (0.57–4.66)	0.946	
CL (l/h)	49.62 (19.28–98.59)	43.60 (23.43–88.67)	47.89 (12.11–102.17)	0.937	
2677G > A/T	GG ($n = 14$)	GA + GT + TA ($n = 32$)	TT ($n = 8$)	GG versus GA + GT + TA versus TT	
C_{max} (μg/ml)	0.91 (0.51–2.66)	1.05 (0.59–3.08)	1.04 (0.55–1.42)	0.82	
AUC_{0-inf} (h μg/ml)	1.08 (0.56–4.66)	0.99 (0.57–2.13)	1.10 (0.60–2.08)	0.92	
CL (l/h)	42.20 (12.11–98.56)	48.09 (19.28–85.18)	45.83 (25.36–102.17)	0.82	
3435C > T	CC ($n = 24$)	CT ($n = 23$)	TT ($n = 7$)	CC versus CT versus TT	
C_{max} (μg/ml)	1.02 (0.51–3.08)	0.98 (0.63–2.00)	1.12 (0.55–1.34)	0.938	
AUC_{0-inf} (h μg/ml)	1.10 (0.56–4.66)	1.01 (0.68–2.08)	0.97 (0.60–1.85)	0.924	
CL (l/h)	45.53 (12.11–98.59)	47.73 (25.10–68.95)	40.63 (27.08–102.17)	0.929	
ABCC2					
*+9383C > G	CC ($n = 4$)	CG ($n = 34$)	GG ($n = 15$)	CC versus CG versus GG	
C_{max} (μg/ml)	1.10 (0.58–1.98)	0.96 (0.55–3.08)	1.06 (0.51–2.66)	0.969	
AUC_{0-inf} (h μg/ml)	1.09 (0.57–1.63)	1.08 (0.57–4.66)	0.99 (0.56–2.14)	0.864	
CL (l/h)	52.59 (31.75–98.59)	46.42 (12.11–102.17)	45.34 (22.04–88.67)	0.739	
ABCG2					
421C > A	CC ($n = 28$)	CA ($n = 21$)	AA ($n = 5$)	CC versus CA versus AA	
C_{max} (μg/ml)	1.05 (0.55–3.08)	1.09 (0.58–2.00)	0.83 (0.51–0.95)	0.067	
AUC_{0-inf} (h μg/ml)	1.01 (0.57–4.66)	1.12 (0.60–2.08)	1.07 (0.56–1.85)	0.706	
CL (l/h)	47.42 (12.11–102.17)	45.72 (23.43–72.00)	43.93 (27.08–98.59)	0.773	
CYP3A5					
*CYP3A5*3*	AA ($n = 4$)	AG ($n = 28$)	GG ($n = 22$)	AA versus AG versus GG	
C_{max} (μg/ml)	1.00 (0.94–1.20)	0.96 (0.51–3.08)	1.10 (0.58–2.66)	0.713	
AUC_{0-inf} (h μg/ml)	1.18 (0.91–1.42)	0.98 (0.56–2.13)	1.02 (0.57–4.66)	0.801	
CL (l/h)	38.44 (31.27–55.21)	47.81 (19.28–102.17)	46.23 (12.11–98.59)	0.829	

[a] Pharmacokinetic data are represented by median (range). C_{max} peak plasma concentration, AUC_{0-inf} area under plasma concentration–time curve from time zero to infinity, *CL* plasma clearance

nadir haemoglobin from cycle 1 baseline compared to those with GG ($n = 14$) or TT ($n = 8$) genotypes [median (range); percentage decrease in nadir haemoglobin from cycle 1 baseline (%); GA + GT + TA vs. GG vs. TT; 9.9 (0.0–26.0) vs. 3.8 (−3.5 to 19.7) vs. 6.2 (−6.3 to 16.8); $P = 0.006$]. A similar trend as above was observed for *ABCB1* rs1045642, with the patients harbouring the heterozygous genotype (CT; $n = 23$) having the highest percentage decrease in nadir haemoglobin from cycle 1 baseline compared to those with CC ($n = 24$) or TT

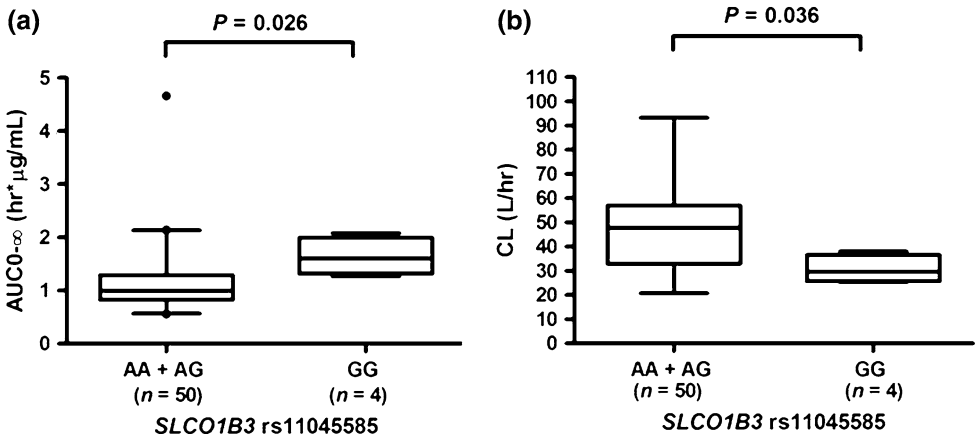

Fig. 2 Influence of *SLCO1B3* rs11045585 (IVS12-5676A > G) on **a** docetaxel AUC_{0-inf} and **b** CL. AUC_{0-inf} area under plasma concentration–time curve from time zero to infinity; *CL* plasma clearance (Whiskers: 5–95 percentile)

($n = 7$) genotypes [median(range); percentage decrease in nadir haemoglobin from cycle 1 baseline (%); CT vs. CC vs. TT; 9.9 (0.0–26.0) vs. 4.6 (−3.5 to 21.7) vs. 5.7 (−6.3 to 17.3); $P = 0.066$]. No significant influences of *ABCB1* variants on pharmacokinetics of docetaxel were observed. *ABCG2* rs2231142 and *ABCC2* rs12762549 had no significant correlation with any of the pharmacokinetic and pharmacodynamic parameters examined.

With regards to *SLCO1B3* rs11045585, patients carrying at least one reference allele (AA + AG) had significantly lower AUC_{0-inf} and higher CL ($P = 0.026$ and $P = 0.036$, respectively; Table 2; Fig. 2a, b, respectively) compared to patients carrying the homozygous variant allele (GG). Patients harbouring the GG genotype also had approximately 10- and 1.5-fold decrease in their nadir platelet counts and haemoglobin compared with patients carrying the AA + GG genotype. These pharmacodynamics effects were non-significant, however.

There were no discernible influences of *CYP3A5* rs776746 on the pharmacokinetics and pharmacodynamics of docetaxel.

Discussion

In the present study, the in vivo influences of the selected polymorphisms in candidate genes across the docetaxel biochemical pathway were evaluated in a cohort of Asian NPC patients in an attempt to understand the genetic causes of interindividual variabilities in docetaxel disposition. Similar to most of the earlier reports, this study could not establish a relationship between *CYP3A5* rs776746 and the pharmacokinetics of docetaxel [17, 18]. Previously, individuals who harboured the *CYP3A4*1A/1B* (rs2740574) and *CYP3A5*1/*3* (rs776746) haplotypes were related to an increase in clearance and/or decrease in exposure of docetaxel [14, 19]. Both rs2740574 and *CYP3A5*1* alleles have been shown to be in substantial linkage disequilibrium in Caucasians and African Americans [14, 20]. Therefore, the observed phenotypic effect might have been due to the simultaneous presence of both alleles. Unfortunately these findings could not be revalidated in the current patient population due to the rarity of the rs2740574 allele in our population [11]. It is unlikely that *CYP3A4* and *CYP3A5* polymorphisms will be of much clinical benefit in affecting docetaxel disposition in Asian patients.

Amongst the three naturally occurring common polymorphisms in *ABCB1*, both rs2032582 and rs1045642 were correlated with a decrease in haemoglobin levels, independent of an effect on systemic exposure. Previous studies have not investigated the association between *ABCB1* variants and haemoglobin level, whilst rs2032582 and rs1045642 were correlated with higher neutropenia grade [19, 21]. The causative reason for the effect of the variant alleles on haemoglobin count may be due to the altered transporter activity of ABCB1 in the local bone marrow tissues. The haematopoietic stem cells in the bone marrow compartment were shown to display ABCB1 transport activity [22], and rs1045642 variation was previously associated with altered rhodamine 123 efflux from the $CD54^+$ natural killer cells [9]. *ABCC2* rs12762549 was also found not to affect the disposition of docetaxel in the present patient group, although it was previously correlated with higher incidence of neutropenia in Japanese patients [23]. In the latter study, there was no mention of the docetaxel schedule in the patients [23]. It is not clear whether the disparity could have been due to differences in the chemotherapy dosing schedule between the study by Kiyotani et al. [23] and the present study. No influence of *ABCG2* rs2231142 on docetaxel disposition was observed, which concurs with the in vitro observations of previous studies [14]. To support this, Brooks et al. [24] aligned the amino acid sequences of both halves of *ABCB1* (transmembrane region 1–6 and 7–12; taxane binding sites) and *ABCG2*

and identified that the latter was not in homology with the first half of the taxane-binding site in ABCB1. This observation greatly elucidated the mechanism underlying the inability of ABCG2 in transporting taxane.

Patients homozygous for the variant allele of *SLCO1B3* rs11045585 had higher docetaxel exposure compared to patients harbouring at least one reference allele. These pharmacokinetic differences between patients in the different genotypic groups could have resulted in the observed non-significant trend towards greater decrease in nadir platelet and nadir haemoglobin from baseline value in cycle 1 in patients harbouring GG genotype. Previously, Kiyotani et al. [23] identified the *SLCO1B3* rs11045585 and *ABCC2* rs12762549 as strong determinants of grade 3 or 4 docetaxel-induced neutropenia in Japanese patients. No pharmacokinetics data of the studied patients were reported, however [23]. It is possible that the rs11045585 may exert its functional effect by being in haplotypic combination with other unknown functional polymorphisms in the *SLCO1B3* gene. In view of the in vivo effect of this intronic SNP, further mechanistic studies are needed to elucidate the biological basis of these observations. A complete screening of the *SLCO1B3* gene would be useful in understanding its haplotype and linkage structure and the functional impact on the disposition of putative drug substrates.

In conclusion, the present exploratory study suggests that the wide degree of interpatient variability in docetaxel treatment in NPC patients probably results from the cooperative influence of functional polymorphisms in *ABCB1* and *SLCO1B3* genes. Docetaxel constitutes an important agent amongst the limited armamentarium of cytotoxics available for treatment of NPC, and understanding the mechanisms responsible for variations in its disposition characteristics will probably aid in improving treatment. Further investigations into other ethnically diverse cancer patient populations for which docetaxel is indicated will probably provide additional mechanistic clues to the observed differences in pharmacokinetics and pharmacodynamics of this important drug.

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Conflict of interest None.

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