UNIVERSITI PUTRA MALAYSIA

PHARMACOGENETICS OF CYP450A, ABCB1, ABCC2, SLCO1B3 GENE POLYMORPHISMS AND PLASMA ALPHA-1-ACID GLYCOPROTEIN LEVEL ON NONHAEMATOLOGICAL ADVERSE EVENTS OF DOCETAXEL IN MALAYSIAN BREAST CANCER PATIENTS

RAFID SALIM JABIR

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By

RAFID SALIM JABIR

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillments of the Requirements for the Degree of Doctor of Philosophy

November 2015

DEDICATION

To my family,
Azeez, Fatima….
Luma,
Jinan, Salim….
Ahlam, Hatem…
Ruaa, Rami…..
Auday, Ahmed and Ali……

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Doctor of Philosophy

PHARMACOGENETICS OF CYP450A, ABCB1, ABCC2, SLCO1B3 GENE POLYMORPHISMS AND PLASMA ALPHA-1-ACID GLYCOPROTEIN LEVEL ON NONHAEMATOLOGICAL ADVERSE EVENTS OF DOCETAXEL IN MALAYSIAN BREAST CANCER PATIENTS

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RAFID SALIM JABIR

November 2015

Chairman : Professor Johnson Stanslas, PhD
Faculty : Medicine and Health Sciences

Docetaxel is an antitubulin chemotherapeutic agent approved for the treatment of breast, lung, ovarian and non-hormonal dependent prostate cancers. However, the success of this drug is limited by adverse events (AEs), the severity of which ranges from tolerable to life threatening. Tapering the dose or changing the regimen would limit the use of docetaxel. Therefore, the present study was conducted involving 110 Malaysian breast cancer patients of different ethnic groups (Malays, Chinese and Indians) to investigate the association between docetaxel AEs and single nucleotide polymorphisms (SNPs) of genes encoding for proteins involved in the metabolism and transport of docetaxel. In addition, the present study investigated the association of plasma levels of alpha-1-acid glycoprotein (AAG) with docetaxel-induced non-haematological AEs. Eligible consented patients enrolled in the study were recruited from University Malaya Medical Centre (UMMC) and Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The ethnicity of breast cancer patients in this study consisted of 40% Malays (n=44), 52% Chinese (n=57) and 8% Indians (n=9). Fatigue (50%), nausea (35%) and oral mucositis (31%) were the most commonly reported non-hematologic AEs. The SNPs of enzyme cytochrome P450 3A5 (*CYP3A5* 6986A>G), and transporters ATP-binding cassette (*ABCB1* 3435C>T, *ABCB1* 2677G>T/A and *ABCC2* 1249G>A) as well as solute carrier organic anion transporter (*SLCO1B3* 334T>G) had significant influence on the development of docetaxel AEs. Rash was significantly associated with *ABCB1* 3435CT polymorphism: 36% of Chinese patients who were carriers of heterozygous genotype developed rash, while it only occurred in 21% of Malay carriers. It is worth noting that the Indians did not develop rash although 44% of them had heterozygous genotype. As such, it can be said that Chinese who are carriers of the heterozygous genotype are at high risk of developing rash. Moreover, since the heterozygous and mutant genotypes showed higher prevalence than the wild type, the toxicity effect

(rash) is very likely related to mutant allele (T). Interestingly, the wild type GG of *ABCB1* 2677GA was associated with fatigue in 60% of Malays, 53% of Chinese and 33% of Indians. However, the difference among the ethnic groups was not statistically significant. Oral mucositis was associated with the coexistence of *CYP3A5* 6986AA (wild type) and *ABCB1* 3435TT (mutant). Low plasma levels of AAG were significantly associated with rash and oral mucositis caused by docetaxel. This study indicates SNPs-AEs associations could be used to individualise treatment to reduce AEs of docetaxel in Malaysian breast cancer patients.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

FARMAKOGENETIK POLIMORFISME GEN CYP450A, ABCB1, ABCC2, SLCO1B3 DAN TAHAP PLASMA GLIKOPROTEIN ALPHA-1-ACID KE ATAS KESAN ADVERS BUKAN HEMATOLOGI DICETUSKAN OLEH DOCETAXEL DIKALANGAN PESAKIT KANSER PAYUDARA MALAYSIA

Oleh

RAFID SALIM JABIR

November 2015

Pengerusi : Profesor Johnson Stanslas, PhD
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Docetaxel ialah agen kemoterapi anti-tubulin yang diluluskan untuk rawatan kanser payudara, paru-paru, ovari dan prostat yang tidak bersandarkan hormone. Walau bagaimanapun, kejayaan ubat ini terhad dengan kesan advers (KA) yang mana tahap keterukannya meliputi kesan yang boleh ditolerasikan sehingga boleh memudaratkan nyawa. Penirusan dos atau penukaran regimen akan mengehadkan penggunaan docetaxel. Oleh itu, bagi mengkaji hubungkait antara KA docetaxel dan polimorfisme nukleotida tunggal (SNP) sebagai gen pengekod protein yang terlibat dalam metabolisme dan pengangkutan docetaxel, seramai 110 pesakit kanser payudara di Malaysia yang berbeza kumpulan etnik (Melayu, Cina dan India) telah melibatkan diri. Di samping itu, kajian ini juga meneliti hubungan antara tahap plasma glikoprotein alpha-1-asid (AAG) dengan kesan sampingan bukan hematologi yang disebabkan oleh docetaxel. Pesakit yang memberi persetujuan untuk melibatkan diri dalam kajian ini direkrut daripada Pusat Perubatan Universiti Malaya (PPUM) dan Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM). Dalam kajian ini, jumlah etnik pesakit kanser payudara adalah terdiri daripada 40% Melayu (n=44), 52% Cina (n=57) dan 8% India (n=9). KA bukan hematologic yang biasa dilaporkan adalah seperti keletihan (50%), mual (3 %) dan mukositis oral (31%). SNP daripada sitokrom enzim P450 3A5 (*CYP3A5* 6986A>G), transporter kaset pengikat ATP (*ABCB1* 3435C>T, *ABCB1* 2677G>T/A dan *ABCC2* 1249G>A), serta transporter bahan larut organik anion (SLCO1B3 334T>G) mempunyai pengaruh yang besar terhadap perkembangan KA docetaxel. Ruam mempunyai kaitan yang ketara dengan polimorfisme *ABCB1* 3435CT: Sebanyak 36% daripada pesakit Cina merupakan pembawa genotip heterozigus yang menghidapi ruam, sementara itu hanya 21% daripada pesakit Melayu yang mendapat ruam. Berbeza dengan pesakit india, mereka tidak mendapat ruam walaupun seramai 44% daripada mereka

mempunyai genotip heterozigus. Oleh itu, boleh dikatakan bahawa pesakit Cina merupakan pembawa genotip heterozigus yang mempunyai risiko tinggi untuk menghidapi ruam. Selain itu, memandangkan keheterozigotan dan genotip mutan juga menunjukkan kelaziman yang lebih tinggi berbanding dengan genotip jenis liar, kesan ketoksikan (ruam) berkemungkinan mempunyai kaitan dengan alel mutan (T). Menariknya, genotip jenis liar GG bagi gene ABCB1 2677GA dapat dikaitkan dengan keletihan di kalangan pesakit Melayu sebanyak 60%, pesakit Cina sebanyak 53% dan pesakit India sebanyak 33%. Walau bagaimanapun, perbezaan antara kumpulan etnik tidak ketara secara statistik. Mukositis oral dapat dikaitkan dengan wujudnya kedua-dua gen *CYP3A5* 6986AA (jenis liar) dan *ABCB1* 3435TT (mutan). Tahap plasma AAG yang rendah menunjukan kaitan yang ketara dengan ruam dan mukositis oral yang berpunca daripada docetaxel. Kajian ini menunjukkan kaitan antara SNP-KA yang boleh digunakan dalam memberikan rawatan secara individual bagi mengurangkan KA yang disebabkan oleh docetaxel kepada pesakit kanser payudara di Malaysia.

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I certify that a Thesis Examination Committee has met on 3 November 2015 to conduct the final examination of Rafid Salim Jabir on his thesis entitled "Pharmacogenetics of CYP450A, ABCB1, ABCC2, SLCO1B3 Gene Polymorphisms and Plasma Alpha-1-Acid Glycoprotein Level on Nonhaematological Adverse Events of Docetaxel in Malaysian Breast Cancer Patients" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Name of Member of Supervisory Committee:	Associate Professor Dr. Rakesh Naidu

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LIST OF ABBREVIATIONS

AAG	Alpha-1-Acid Glycoprotein
ABC	ATP-Binding Cassette
AEs	Adverse Events
AUC	Area Under Curve
BSA	Body Surface Area
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ELISA	Enzyme Linked Immune-Sorbent Assay
HSA	Human Serum Albumin
HWE	Hardy-Weinberg Equilibrium
LD	Linkage Disequilibrium
MDR	Multidrug Resistance Protein
MRP	Multidrug Resistance-Associated Protein
OATP	Organic Anion-Transporting Polypeptide
ORM	Orosomucoid
PCR-RFLP	Polymerase Chain Reaction- Restriction Fragment Length Polymorphism
P-gp	P-glycoprotein
RT	Radiotherapy
SLCO	Solute Carrier Organic Anion
SNPs	Single Nucleotide Polymorphisms
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
UMMC	Universiti Malaya Medical Centre
UPM	Universiti Putra Malaysia

CHAPTER 1

INTRODUCTION

1.1 Background

Cancer treatment is one of the greatest challenges in therapy domain. The notion of chemotherapy use in cancer treatment started at the beginning of the 20th century, when chemicals screening in rodents' transplantable tumour models was used to improve and limit the list of chemicals that may affect the disease progression.

The effects of drugs produced and developed under World War II research related programs triggered the establishment of the United States of America (USA) national drug development effort in 1955 which ultimately led to the formation of the Cancer Chemotherapy National Service Centre in the US. The optimistic view on potential cancer treatment with chemotherapies was overwhelmed by the success of curing acute childhood leukaemia and advanced Hodgkin's disease using combination chemotherapy. It paved the way for adjuvant chemotherapy study and enhanced the US national cancer program. Nowadays, assessment of molecular level changes in the screening and development of potential new drugs had altered the understanding, impact and application of chemotherapy (DeVita and Chu, 2008).

Taxanes group of drugs which includes paclitaxel, docetaxel and cabazitaxel stood out among the useful antineoplastic agents used by oncologists for the treatment of cancer. Docetaxel had shown success as a single agent (Argiris et al., 2013) and in combination therapy (Ueda, et al., 2013), at the neoadjuvant (Yao et al., 2012), adjuvant and metastatic settings (Goble and Bear, 2003). However, docetaxel was approved for the treatment of early stage, locally advanced and/or metastatic breast, non-small cell lung and androgen-independent metastatic prostate cancers (Michael et al., 2009; Bosch et al., 2006).

Docetaxel is an antimitotic semisynthetic compound, derived from 10-deacetylbaccatin III, which is isolated from the European yew tree, *Taxus baccata* (Joseph and Jean, 2004). It binds to the β subunit of tubulin, eventually interfering with microtubule depolymerization process leading to cell cycle arrest at the G2/M phase (Gligorov and Lotz, 2004; Tanaka et al., 1996). The arrested cells then undergo apoptosis (Domuntet and Sikic, 1999).

Docetaxel has high affinity to bind plasma proteins (>95%) and the clinically active part is the free unbound form (Baker et al., 2005). Principally, docetaxel binds to plasma alpha-1-acid glycoprotein (AAG), lipoprotein and albumin (Urien et al., 1996). Chronic inflammation and advanced cancer often cause elevation in AAG

which is an acute phase protein. A study showed individual variation in docetaxel toxicity was due to variation in AAG levels (Bruno et al., 1998).

Metabolism of docetaxel occurs through cytochrome P450 (CYP), especially CYP3A4 (Jibodh et al., 2013), which is also involved in metabolism of many other anticancer drugs. CYP3A is the most abundant enzyme expressed in the human liver and intestine. The function of CYP can be affected by several factors including genetic polymorphisms, environmental factors, changes in physiological conditions such as age and drug-drug or drug-food interactions. Inter-individual differences in pharmacokinetic profiles of anticancer agents have been implicated in the variation ofdrug efficacy and/or toxicity (Figg and Chau, 2006).

Docetaxel as a first line single agent treatment of advanced breast cancer, had shown a dose effect relationship at doses 75-100 mg/m2, where overall response rate (ORR) was 67.7% to 100 mg/m2 of docetaxel (Chevallier et al., 1995), while the ORR was 53%-57% when docetaxel was given as a second line of treatment in anthracyclin resistant patients (Valero et al., 1995; Ravdin et al., 1995). Clinical response and dose relationship of docetaxel given at (60, 75 and 100 mg/m2) every 3 weeks in patients with advanced breast cancer as a second line treatmentrevealed obvious tumour response, but higher dose caused higher haematological and non-haematological toxicities without dose-response relationship shown by the overall survival (Harvey et al., 2006). In the first line metastatic breast cancer setting, docetaxel showed improved efficacy (100 mg/m2 every 3 weeks) with a response rate of 48%, compared to the good response to doxorubicin (75 mg/ m2 every 21 days) with a response rate of 33% (Chan et al., 1999).

Although docetaxel is clinically very active and prescribed for a wide spectrum of cancers (Yared and Tkaczuk, 2012), its use is limited mainly by the high risk of development of adverse events (AEs), which usually leads to either dose reduction or diversion of treatment regime (Lee and Swain, 2006). A previous study showed there was an interindividual variation in docetaxel pharmacokinetics which had caused haematological toxicity (Goh et al., 2002). A major challenge in docetaxel therapy is the unpredictable interindividual variation in efficacy and toxicity. This can be caused by renal and hepatic function impairment, variability in disease pathogenesis and severity, and drug interactions (Evans and McLeod, 2003). Despite the potential importance of these clinical variables in determining drug effects, it is recognised that inherited differences in metabolism and excretion can have an even greater effect on drugs response (Evans and McLeod, 2003). It has been postulated and investigated that Single Nucleotide Polymorphisms (SNPs) of genes encoding for enzymes and proteins involved in the metabolism and clearance of drugs may lead to impaired metabolism and and consequent reduced drug efficacy. However, reduced drug clearance may lead to drug accumulation and development of AEs. The influence of those SNPs on the encoded proteins could be a mainsource of the variability in drug toxicity and efficacy (Umamaheswaran et al., 2014).

Drug transporters located on the hepatic cellular membrane play an essential role in the clearance of docetaxel. ATP-binding cassette (ABC) proteins, ABCB1 (also known as MDR1 and P-gp) and ABCC2 (also known as MRP2) (Auner et al., 2010; Dean et al., 2007) as well as solute carrier organic anion transporters (SLCO1B3) (Oshiro et al., 2009) are intimately related to docetaxel uptake and clearance (Jabir et al., 2012). ABCB1 is important in intestinal absorption and biliary excretion (van Zuylen et al., 2000 and 2002), whereas ABCC2 and SLCO1B3 have mutual assisting tasks in the docetaxel transport process in the liver (Cui et al., 2001). SNPs of genes encoding for the above transporters cause loss of function or reduce activity and consequently decrease elimination of the drugs leading to development of toxicity such as neutropenia, diarrhoea and oral mucositis (atrophy and break down of the mucosal lining of the mouth with ulcer formation) in patients receiving chemotherapy (Chang et al., 2010). Therefore, upon identification and validation of SNPs that are strongly associated with a risk of developing toxicity, pharmacogenetic tests could be established to determine if patients are suitable for docetaxel. This way, the treating oncologists would be able to predict the toxicity of the drugs before starting chemotherapy and would allow prescription of right dosage for each patient.

1.2 Problem statement

The dose of docetaxel given in cancer treatment is calculated based on body surface area which is obtained from patient's weight and height. However, patients receiving docetaxel are show variation in type and severity of AEs.

1.3 Hypotheses

1. Gene polymorphisms encoding for enzymes and proteins involved in docetaxel metabolism and transport affect the pharmacodynamic properties of docetaxel in breast cancer patients.
2. There are inter-ethnic variations in pharmacodynamics (AEs) of docetaxel.
3. Plasma level of docetaxel carrier (AAG) in the circulation is correlated with docetaxel AEs.

1.4 Objectives

1.4.1 General objective

To investigate the association between SNPs of genes encoding for enzymes and proteins involved in the metabolism and transport of docetaxel and pharmacodynamics (non-haematological AEs) variations in Malaysian breast cancer patients in adjuvant and metastatic settings.

1.4.2 Specific objectives

1. To determine the variations in AEs induced by docetaxel among breast cancer patients.
2. To determine inter-ethnic (Malay, Chinese and Indians) variations in docetaxel AEs.
3. To determine SNPs of enzymes involved in docetaxel metabolism (CYP3A4 and CYP3A5) and transport (ABCB1, ABCC2 and SLCO1B3) and their associations with docetaxel-induced AEs.
4. To determine the relationship between plasma level of AAG and AEs of docetaxel.

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