RESEARCH ARTICLE

Editorial Process: Submission:11/01/2017 Acceptance:09/24/2018

Effects of *ABCC2* and *SLCO1B1* Polymorphisms on Treatment Responses in Thai Metastatic Colorectal Cancer Patients Treated with Irinotecan-Based Chemotherapy

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Abstract

Purpose: Irinotecan is an anticancer medicine which is used mostly in metastatic colorectal cancer (mCRC) treatment as second or third line chemotherapy. Several factors affect its efficacy and toxicity, including pharmacogenomics. This study aimed to investigate the impacts of *ABCC2* and *SLCO1B1* polymorphisms on treatment responses in irinotecan-based chemotherapy in 49 Thai mCRC patients. **Materials and Methods:** Forty-nine participants with mCRC enrolled in this study received irinotecan-based chemotherapy from January to June 2017. Genotypic analyses of *ABCC2* (C>T, rs717620) and *SLCO1B1* (A>G, rs2306283) were performed. Treatment responses were evaluated after at least three cycles of chemotherapy were given. **Results:** Allele frequencies of *ABCC2* (C>T) and *SLCO1B1* (A>G) were found at 18.37% and 78.57%, respectively. Neither was associated with treatment responses. However, combined genotypes of *ABCC2* and *SLCO1B1* tended to be associated with clinical benefits in terms of partial responses (PR) and stable disease (SD). All patients (100%) with at least one variant allele of *SLCO1B1* and *ABCC2* were in a PR or SD group, while patients with other genotypes had progressive disease (PD) at 45.5% to 70%, (p = 0.059). **Conclusion:** The combined effect of *ABCC2* and *SLCO1B1* polymorphisms tended to be associated with treatment responses in irinotecan-based treated mCRC patients. Therefore, such polymorphisms could be factors impacting inter-individual variation of irinotecan efficacy in Thai mCRC patients.

Keywords: Metastatic colorectal cancer- *ABCC2*- *SLCO1B1*- irinotecan

Asian Pac J Cancer Prev, **19 (10)**, 2757-2764

Introduction

Colorectal cancer (CRC) represents as one of the most prevalent and deadly tumor types with worldwide mortality rates continuing to rise. The World Health Organization (WHO) reported the incidence of CRC cases at approximately 1.36 million new cases and 0.69 million deaths in 2012 (Hashim et al., 2016). In Thailand, the crude rate of CRC was 9 per 100,000 in males and 7 per 100,000 in females. Half of these patients presented with advanced stage CRC (28.9% with TNM stage 3 and 38.8% TNM stage 4, respectively). Nearly 90% of patients diagnosed early who receive optimized therapy can be expected to survive 5 years while the overall survival rate of metastatic colorectal cancer (mCRC) patients is only 5% (Phiphatpatthamaamphan and Vilaichone, 2016).

Chemotherapy is the main treatment for mCRC (Benson et al., 2017). Irinotecan is an anticancer drug that inhibits topoisomerase I, which is approved for mCRC treatment in combination with 5-fluorouracil and folinic acid in a first line treatment setting or as a monotherapy in the second line setting. The overall response rate of irinotecan-based regimens was from 30-50% (Colucci et al., 2005; Toumigand et al., 2004). However, severe adverse events such as diarrhea (20%) and neutropenia (34%) lead to dose reduction, early cessation of treatment, or death (Fuchs et al., 2003). The severity of these adverse events is related to a high concentration of 7-ethyl-10-hydroxycamptothecin or SN-38, the active metabolite of irinotecan. SN-38 is conjugated with glucuronic acid by hepatic and extra hepatic Uridine 5'-diphosphate-glucuronosyltransferase (UDP- glucuronosyltransferase or UGT), changing SN-38 to SN-38G, the inactive metabolite of irinotecan. Therefore, the efficiency of SN-38 glucuronidation and transport relies heavily on *UGT1A* enzymes and drug transport activity.

Many studies have been conducted to explain predictive factors for adverse events in irinotecan chemotherapy. One very well-known factor is genetic polymorphisms of UGT, a phase II drug metabolizing enzyme involved in SN-38 detoxification which is associated with differences

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in toxicity from irinotecan-based treatment regimens. In irinotecan pharmacogenomic studies, it is observed that Caucasian patients carrying the *UGT1A1*28* allele are at increased risk of severe neutropenia (Liu et al., 2014). The other variant *UGT1A1*6* (211G>A, rs4148323) which is commonly found in East Asians while rarely detected in Caucasians and Africans is also associated with reduced *UGT1A* enzyme function (Minami et al., 2007).

The regulatory status and other issues around irinotecan therapy are based on cumulative evidence of the association of *UGT1A1* genotypes with severe toxicity, especially neutropenia, which has led to the clinical use of a diagnostic kit for the *UGT1A1*28* allele in the US (August, 2005). Subsequently, the same practice was considered for the clinical use of a diagnostic kit for *UGT1A1*28* and **6* alleles in Japan (March, 2009).

Although variability in irinotecan pharmacokinetics and pharmacodynamics has been partially described for *UGT1A* variants, allele frequencies of *UGT1A1*28* and *UGT1A1*6* still slightly detected in Thai mCRC were 12.5% and 8%, respectively, they do not fully explain the reason for the subgroups of non-carrier patients who may experience irinotecan-induced toxicity and non-responders to treatment (Atasilp et al., 2016).

In addition to the UGT family, many other enzymes are involved in irinotecan metabolism. The ATP-binding cassette (ABC) and solute-carrier (SLC)family of transporters can also modulate irinotecan pharmacokinetic and pharmacotdynamic effects. Irinotecan, SN-38 and SN-38G are transported out of the cell into bile by members of the ABC transporter family especially *ABCC2*, while *SLCO1B1* is a major influx transporter. *SLCO1B1* is associated with the uptake of SN-38 from the blood to be transported to the liver (Haenisch et al., 2007). Therefore, genetic variations of *ABCC2* and *SLCO1B1* are suspected of influencing inter-individual variability which could impact treatment responses to irinotecan-based chemotherapy.

In Asians, allele frequency T of *ABCC2* detected at a high allele frequency (approximately 20%) in advanced colorectal cancer (Fujita et al., 2008). Previous studies have demonstrated that *ABCC2* polymorphism was associated with the specific pharmacokinetics of SN-38, which may account for overall irinotecan treatment response rates. Almost 20% of mRNA showed reduced activity in whom with *ABCC2* variant gene in kidney cortex tissue of nephrectomized renal cell cancer patients (Haenisch et al., 2007). *ABCC2* polymorphism was statistically significant with increased SN-38 exposure in terms of the area under the curve of time and concentration (Akiyama et al., 2012). However, several recently published studies have provided conflicting data. Metastatic colorectal cancer patients without *ABCC2* (rs717620, C>T) had increased overall response rate and median progression-free survival (PFS) (P = 0.031) (Fujita et al., 2008). In contrast, in a study of Singaporean nasopharyngeal carcinoma patients, *ABCC2* polymorphism resulted in a reduced irinotecan plasma concentration time curve (AUC) compared with the CC genotype (Zhou et al., 2005).

The allele frequency G of *SLCO1B1*1b* is also high in Asians (about 64.7-75%) (Fujita et al., 2008; Huang et al., 2013). The *SLCO1B1*1b* polymorphism was associated with increased enzyme function, leading to increased hepatic uptake of SN-38 from plasma to human (Nozawa et al., 2005). A previous study stated that the *SLCO1B1* rs2306283 polymorphism significantly increased tumor response and presented a rapid response rate in patients with the GA/AA genotype. The response rate of these patients was higher than in patients with the homozygous wild genotype (G/G) (odds ratio [OR] =3.583, 95%CI =1.301-9.871, P = 0.011). Furthermore, the GA/AA genotype was associated with a better PFS (hazard ratio =0.402, 95% CI = 0.171-0.945, P = 0.037) (Teft et al., 2015). This finding contrasts with another study which found significantly increased PFS in patients with the G/G genotype when compared with patients carrying at least one wild-type allele (HR=1.60, 95% CI=1.04-2.46) (Teft et al., 2015).

At present, no studies have explored the association between *ABCC2* and *SLCO1B1*1b* polymorphisms on treatment response in Thais with CRC. Therefore, the aim of the present research was to investigate the impacts of *ABCC2* and *SLCO1B1* polymorphisms on treatment responses to irinotecan-based chemotherapy in Thai mCRC patients.

Materials and Methods

Patients and Data Collection

Forty-nine patients with mCRC were enrolled in this prospective cohort study. All participants received irinotecan-based chemotherapy from January to June 2017 at the outpatient oncology department of King Chulalongkorn Memorial Hospital (KCMH) in Bangkok, Thailand. The inclusion criteria were: patients with mCRC confirmed by histopathology or cytology; over 18 years of age; an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; scheduled to receive irinotecan-based chemotherapy of at least 3 cycles. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine at Chulalongkorn University, Bangkok, Thailand (IRB number 699/59). All patients signed an informed consent document which is in accordance with ethical standards laid down in the 1964 Declaration of Helsinki.

Demographic and other relevant clinical data were collected from patient medical records.5 ml of peripheral blood was collected from each subject by a professional nurse and stored in EDTA tubes. Genomic DNA was extracted from blood samples using a QIAIamp blood kit (QAIGEN Gmbh, Hilden, Germany). Analysis of the *ABCC2* (C>T), rs717620 and *SLCO1B1*1b* (388A>G), and rs2306283 genotypes was performed using real-time polymerase chain reaction restriction (qPCR) with Taqman genotyping assay. After PCR amplification, endpoint plates were read on a StepOnePlus Real time PCR System (Applied Biosystem Inc., Foster City, CA USA). Using fluorescence measurements made during plate readings, the SDS software plots Rnvalues based on the fluorescence signals from each well then determines which alleles were in each sample.

Treatment response was an objective tumor response which was classified according to Response Evaluation Criteria in Solid tumors (RECIST) criteria, version 1. Treatment response was evaluated after completing at least 3 cycles. A responder was a patient who had a partial response (PR) or complete response (CR) and other patients who had progressive disease (PD) or stable disease (SD) were classified as non-responders. Nonetheless, patients with PR or CR or SD were considered as groups with clinical benefit.

Irinotecan-based chemotherapy regimens given in this study, following physician recommendations, were:

Single irinotecan regimen

125 or 300mg/m^2, 90 minute intravenous irinotecan infusion on day 1;

Irinotecan plus capecitabine regimen

125-300mg/m^2, 90 minute irinotecan intravenous infusion on day 1; 2,000 mg/m^2 of capecitabine from day 1-14;

IFL regimen

125-150 mg/m^2, 90 minute intravenous irinotecan infusion on day 1; 20 mg/m^2 intravenous leucovorin (LV) infusion on day 1; 500 mg/m^2 intravenous fluorouracil as a bolus on day 1 repeated every 2 weeks;

Irinotecan+other

5 mg/kg intravenous bevacizumab infusion once every 2weeks; 125 mg/m^2, 90 minute intravenous irinotecan infusion on day1; 20 mg/m^2 intravenous leucovorin infusion on day 1; 500 mg/m^2 intravenous fluorouracil as a bolus on day 1 repeated every 2 weeks; or Cetuximab 400 mg/m^2 intravenous infusion on day 1; 125 mg/m^2, 90 min intravenous irinotecan Infusion on day 1; 20 mg/m^2 intravenous leucovorin infusion on day 1; 500 mg/m^2 intravenous fluorouracil as a bolus on day 1 repeated every 2 weeks.

Statistical Analysis

Baseline characteristics of demographic data are shown as means ± standard deviation (SD) for continuous variables and number of participants (%) for category variables. The association between *ABCC2* and *SLCO1B1* polymorphisms on treatment response were analyzed by Chi-squared test or Fisher's exact test. Statistical tests provided two sides. The p value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 22.0 (SPSS. Co., Ltd., Bangkok, Thailand).

Results

Patient Characteristics

Forty-nine participants were included in this study. Patient characteristics are shown in Table 1. Thirty-two (65.3%) participants were male and 17 (34.7%) were female. The average age was 59.6 ± 12.2 years. Adenocarcinoma with moderated differentiated histology was the most common cancer found in 21 patients

Table 1. Patient Characteristics and Treatment Response

Characteristic	N (%)	
Total number of participants	49	
Age(mean ± SD)	59.57±12.23 (26,81)	
Characteristic	N	%
Gender		
Male	32	65.3
Female	17	34.7
Performances status		
ECOG score=0	4	8.2
ECOG score=1	45	91.8
Histology		
well differentiated	19	38.8
moderately differentiated	21	42.9
poorly differentiated	6	12.2
No data	3	6.1
Primary tumor site		
Colon	18	36.7
Sigmoid	15	30.6
Rectum	16	32.7
Metastatic site		
Liver	10	20.4
Lung	6	12.2
other (eg. peritoneal, pelvic, bladder, ovarian, spleen, ovary, bone)	8	16.3
lung and liver	14	28.6
liver or lung+other	11	22.4
Treatment line		
first line	7	14.3
Second line	32	65.3
>second line	10	20.4
Treatment regimen		
Irinotecan	5	10.2
Irinotecan+capecitabine	9	18.4
IFL	31	63.3
Irinotecan+other	4	8.2
Irinotecan dose		
100-125 mg/m^2	25	51
150 mg/m	21	42.9
180 mg/m^2	3	6.1
ABCC2 genotype		
C/C	32	65.3
C/T	16	32.7
T/T	1	2.0
SLCO1B1 genotype		
A/A	5	10.2
A/G	11	22.4
G/G	33	67.3
Responder		
Complete response (CR)	0	0
Partial response (PR)	5	10.2
Non-responder		
Stable disease (SD)	22	44.9
Progressive disease (PD)	22	44.9

ECOG, Eastern Cooperative Oncology Group.

Table 2. Association between Factors and Overall Response

Total number of participants = 49					
Factor	N	Overall response*		χ^2 value	P-value
		PR (%)	SD + PD (%)		
Gender				0.069	1.000
Male	32	3 (9.4)	29 (90.6)		
Female	17	2 (11.8)	15 (88.2)		
Age(years)				0.668	0.639
≤ 60 years	28	2 (7.1)	26 (92.6)		
>60 years	21	3 (14.3)	18 (85.7)		
ECOG status				1.041	0.359
0	4	1 (25)	3 (75)		
1	45	4 (8.9)	41 (91.1)		
Histology				3.759	0.289
Well differentiated	19	3 (15.8)	16 (84.2)		
Moderately differentiated	21	1 (4.8)	20 (95.2)		
Poorly differentiated	6	0 (0)	6 (100)		
No data	3	1 (33.3)	2 (66.7)		
Primary tumor site				0.677	0.713
colon	18	1 (5.6)	17 (94.4)		
sigmoid	15	2 (13.3)	13 (86.7)		
rectum	16	2 (12.5)	14 (87.5)		
Metastatic site				5.813	0.214
liver	10	2 (20)	8 (80)		
lung	6	0 (0)	6 (100)		
other (eg.peritoneal, pelvic, bladder, ovarian, spleen, ovary, bone)	8	0 (0)	8 (100)		
lung and liver	14	3 (21.4)	11 (78.6)		
liver or lung+other	11	0 (0)	11 (100)		
Treatment line				3.124	0.210
first line	7	2 (28.6)	5 (71.4)		
second line	32	2 (6.3)	30 (93.7)		
>second line	10	1 (10)	9 (90)		
Number of metastatic sites				1.899	0.387
1	19	2 (10.5)	17 (89.5)		
2	19	3 (15.8)	16 (84.2)		
>2	11	0 (0)	11 (100)		
Previous treatment				1.426	0.699
Chemotherapy	4	1 (25)	3 (75)		
Surgery+chemotherapy	30	3 (10)	27 (90)		
Surgery+radiotherapy+chemotherapy	11	1 (9.1)	10 (90.9)		
Radiotherapy+chemotherapy	4	0 (0)	4 (100)		
Treatment regimen				10.548	0.014*
Irinotecan	5	0 (0)	5 (100)		
Irinotecan+capecitabine	9	2 (22.2)	7 (77.8)		
IFL	31	1 (3.2)	30 (96.8)		
Irinotecan+other	4	2 (50)	2 (50)		
Irinotecan dose				11.499	0.003*
100-125mg/m^2	25	1 (4)	24 (96)		
150mg/m^2	21	2 (9.5)	19 (90.5)		
180mg/m^2	3	2 (66.7)	1 (33.3)		

Table 2. Continued

Total number of participants = 49					
Factor	N	Overall response*		χ^2 value	P-value
		PR (%)	SD + PD (%)		
ABCC2				0.531	0.646
CC	32	4 (12.5)	28 (87.5)		
CT,TT	17	1 (5.9)	16 (94.1)		
SLCO1B1				0.405	1.000
AA,AG	16	1 (6.3)	15 (93.7)		
GG	33	4 (12.1)	29 (87.9)		

ECOG, Eastern Cooperative Oncology Group. *Treatment response was an objective tumor response which was classified according to RECIST criteria.

Table 3. Association between Genetic Polymorphism and Clinical Benefit in Combined Genotype (*ABCC2* and *SLCO1B1*1b*)

Total number of participants 49						
Allele *SLCO1B1*	Allele *ABCC2*	N	Clinical benefit		χ^2 value	P-value
			PR + SD (%)	PD (%)		
AA+AG	CC	10	3 (30)	7 (70)	7.440	0.059*
	CT + TT	6	6 (100)	0 (0)		
GG	CC	22	12 (54.5)	10 (45.5)		
	CT + TT	11	6 (54.5)	5 (45.5)		

(42.9%). Eighteen patients (36.7%) had a primary tumor site in the colon while fourteen patients (28.6%) had metastasis to the lung and liver. Most patients received irinotecan-based chemotherapy as a second line treatment (30 patients, 65.3%). Most participants had a good performance status represented by an ECOG score of 0 and 1.

ABCC2 genotype frequencies

Allele frequencies of *ABCC2* polymorphism (C>T, rs717620) was found at a rate of 18.37 %. The wild type (C/C), heterozygous (C/T) and homozygous variants (T/T) were 65.3 %, 32.7 %, and 2.0 %, respectively.

SLCO1B1 genotype frequencies

Allele frequencies of the *SLCO1B1* polymorphism (A>G, rs2306283) was found in 78.57 %. The wild type (A/A), heterozygous variant (A/G) and homozygous variants (G/G) were found in 10.2 %, 22.4 %, and 67.3 %, respectively.

The allele frequencies of SNPs in the *ABCC2* and *SLCO1B1* genes were tested with Hardy-Weinberg equilibrium. Significant differences were found between the observed and estimated frequencies of the *SLCO1B1* genotype (χ^2 test= 3.933 P= 0.047), while no significant difference was found in the *ABCC2* genotype (χ^2 test= 0.059, P=0.807).

Patient characteristics and treatment responses

Treatment response was an objective tumor response which was classified according to RECIST criteria. A responder was a patient who had a partial response (PR) or complete response (CR) and other patients who had progressive disease (PD) or stable disease (SD) were classified as non-responders. Complete responses were not seen in this study. Only 5 patients (10.2 %) had a partial response. There were no statistically significant differences in the overall response rate according to gender, age, histology, primary tumor site, metastatic site, treatment line, and number of metastatic sites, previous treatments, performance status, alcohol status, or smoking status. Significant differences in treatment response were found only in each treatment regimen and irinotecan dose levels.

The association of ABCC2 and SLCO1B1 polymorphisms on overall response

Overall response rate among different genotypes of *ABCC2* are described in Table 2. Patients with the homozygous wild genotype (CC) had a higher of overall response (12.5% vs. 5.9%) when compared with

Table 4. Association between Genetic Polymorphism and Anemia in Patients with the *SLCO1B1* Polymorphism

Total number of participants 49						
Gene	genotype	N	Anemia after cycle 2		χ^2 value	P-value
			Grade 0-2	Grade 3-4		
SLCO1B1	AA	5	4 (80)	1 (20)	8.983	0.011*
	GA	11	11 (100)	0 (0)		
	GG	33	33 (100)	0 (0)		

Table 5. Association between Genetic Polymorphism and Severe Diarrhea in Patients with the *SLCO1B1* Polymorphism

Total number of participants 49						
Gene	genotype	N	Diarrhea after cycle 1		χ^2 value	P-value
			Grade 0-2	Grade 3-4		
SLCO1B1	AA	5	4 (80)	1 (20)	8.983	0.011*
	AG	11	11 (100)	0 (0)		
	GG	33	33 (100)	0 (0)		

the CT and TT genotypes. However, there were no statistically significant differences.

For *SCLO1B*1, participants with the homozygous variant type (GG) of *SLCO1B1**1b tended to have a higher response rate (12.1% and 6.3%) than patients with other genotypes but there was no statistical association between genetic polymorphisms and overall response rate.

Association of ABCC2 and SLCO1B1 polymorphisms to clinical benefit

Since complete response was not seen in this study, and only around 10% of participants had partial response to chemotherapy. Patients with stable diseases were considered as the part that received treatment benefit from chemotherapy given in term of longer progressive free duration while compared to those with disease progression. Therefore, we combined PR and SD in the same group of patients received clinical benefit from the treatment. When considering the combined genotypes of both genes, the results revealed that patients with the T/T, C/T genotypes of *ABCC2* and the A/A, A/G genotypes of *SLCO1B1* tended to have higher clinical benefit rates (P=0.059), as shown in Table 3.

In term of adverse events, the risk of severe anemia was higher in patients with the homozygous wild type (AA) of *SLCO1B1* (20% and 0%) than in patients with other genotypes (P=0.011). The *SLCO1B1* polymorphism also had an impact on non-hematologic toxicity as the rate of severe diarrhea was significantly higher in patients with the homozygous wild type (AA) (20% and 0%) than patients with other genotypes (P=0.011) as shown in Table 5.

Discussion

Association between UGT polymorphisms and irinotecan toxicities was well recognized since this drug recently approved and regularly used worldwide. Some authorities advise to perform genotypic testing prior to use this drug as mentioned earlier. However, Thai FDA does not provide any recommendation for genotypic testing, lower prevalence as approximately 8% and 12% of problematic genotypes (*UGT1A1*6* and *UGT1A1*28*, respectively) might be the reason (Atasilp et al., 2016). Though, complexity of irinotecan metabolic pathway, many of interesting drug metabolizing and transporting enzymes are still not well understood and need to clarify like *ABCC2* and *SLCO1B1* in our study.

In this study, the prevalence of *ABCC2* and *SLCO1B1* polymorphisms is reported and the impact of each genetic polymorphism on treatment response in Thai mCRC patients was investigated. The prevalence of *ABCC2* of allele C→T rs717620 is found in 15-32% of the Caucasian population and 0% of the African population while a report from a study on Asians showed that allele T contributed 20.5% to advanced colorectal cancer in Japanese subjects (De Jong et al., 2007; Innocenti et al., 2009; Fujita et al., 2008). Our study reports the allele frequency T in Thai mCRC patients at 18.37% which is slightly lower than in the Japanese. The prevalence in *SLCO1B1*1b* of allele A→G rs2306283 was found to be 45% in the Caucasian population and 9% in Africans whereas a much higher rate, reaching 64.7-75% of allele frequency G, was found in Asians (Innocenti et al., 2009; Fujita et al., 2008; Huang et al., 2013). In Thais, this study found the allele frequency G of *SLCO1B1**1b at 78.57% which is higher than previously reported.

Previous studies have explained the relationship between the *ABCC2* polymorphism and overall chemotherapy response rate in Asians. Patients with the C/C genotype at -24 in *ABCC2* showed an increased overall response rate to those with the C/T plus T/T genotype at 52.5% and 23.8%, respectively (P = 0.031) (Fujita et al., 2008). Similar to our study, patients with the homozygous wild genotype (CC) tended to have a higher rate of overall response (12.5% vs. 5.9%) than patients with the CT and TT genotypes though this was not statistically significant (P=0.646). In contrast, As Han (2007) reported in previous work significant tumor response rate in patients with T/T genotypes (P = 0.031) (Watanabe et al., 2009). Previous studies had reported an association between the *SLCO1B1* polymorphism and tumor response. For example; As Huang et al., (2013) showed in previous work patients with GA/AA genotypes had significantly higher and more rapid tumor response rates than patients with the G/G genotype (P = 0.011) (Teft et al., 2015). On the other hand, our study found a contrary result, with a higher overall response rate in patients with the G/G genotype though this was not statistically significant. This result is in accordance with previous study reported patients with homozygous *SLCO1B1* (388G/G) had significantly increased PFS compared with wild types (HR=1.60, 95% CI=1.04-2.46) (Teft et al., 2015).

As Di Martino et al., (2011) reported in previous work, 3 in 9 mCRC patients with the G/A genotype group suffered severe (grade ≥ 3) GI toxicity, while 14 of 17 patients in the other group had no GI toxicity (P = 0.027) which was consistent with our study which found a statistically significant difference in grade 3-4 severe diarrhea in patients with the AA genotype who underwent chemotherapy when compared to others

(P=0.011) (Teft et al., 2015). This study was the first to determine an association when considering the combined genotype of both genes and treatment response. Combining effects of *ABCC2* and *SLCO1B1*1b* genotype might be one explanation for inter-individual variability on treatment response of irinotecan-based chemotherapy. Our results demonstrated the trend of association of at least one variant allele (T/T, C/T) of *ABCC2* and at least one variant allele (A/A, A/G) of *SLCO1B1*1b* and the clinical benefit to irinotecan-treated patients (P=0.059). Several factors might impact the treatment response such as prior chemotherapy regimen, but except dose level of irinotecan and combined genotypic effect of *ABCC2* and *SLCO1B1*1b*, there was no other significant association.

The strength of our study was its prospective design. However, when it come to the stratification that have been done in Table 3-5, the association between *ABCC2* and *SLCO1B1*1b* polymorphisms, clinical benefit and severe toxicity in mCRC with irinotecan-based chemotherapy, the relatively small sample led to a small number of patients in each genotype group which accounted for the weak power of statistical results. Future studies with a larger sample size and more homogeneous treatment pattern should be conducted to elucidate the significance of these genetic polymorphisms on treatment response prior to concluding whether these genetic polymorphisms impact treatment outcomes.

In conclusion, this is the first study to determine the association between *ABCC2* and *SLCO1B1*1b* polymorphisms with respect to treatment response of irinotecan-based chemotherapy in Thai mCRC patients. Our results indicated that *ABCC2* and *SLCO1B1* polymorphisms were not associated with any particular treatment response of irinotecan-based chemotherapy, while the combined effect of both genes tended towards clinical benefit. Therefore, polymorphisms of drug efflux and influx associated genes such as *ABCC2* and *SLCO1B1*1b* might be important factors which can influence inter-individual variability on chemotherapy response in irinotecan-based chemotherapy for some cancer patients.

Conflict of intereststatement

The authors declared no conflict of interest.

Acknowledgements

Research grant funds have been provided for this study by the 90th Anniversary Chulalongkorn University Fund (Ratchadapiseksomphot Endowment Fund).

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