



ABCG2 rs2231142 polymorphism is related to sunitinib-induced toxicity in metastatic renal cell carcinoma: a systematic review

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Background: To summarize and clarify the association between ATP-binding cassette sub-family G member 2 (ABCG2) rs2231142 polymorphism and sunitinib-induced toxicity in metastatic renal cell carcinoma (mRCC).

Methods: A total of 6 studies including 698 patients were analyzed in this systematic review after screening the databases of PubMed, EMBASE and Web of Science. We used odds ratios (ORs) with 95% confidence interval (CI) to evaluate the strength of the association.

Results: It was suggested that rs2231142 was related with the sunitinib-induced toxicity of thrombocytopenia (n=2), neutropenia (n=2), hand-foot syndrome (n=2), fever (n=1) and any hematologic toxicity > grade 2 (n=1). However, such connection was not observed in some articles about thrombocytopenia (n=1), neutropenia (n=1) or hand-foot syndrome (n=1). Furthermore, the associations between rs2231142 and diarrhea (n=1), hypertension (n=1), hypothyroidism (n=1), leucopenia (n=1) and proteinuria (n=1) were not detected.

Conclusions: Our systematic review suggested that rs2231142 is associated with sunitinib-induced toxicity in metastatic renal cell carcinoma.

Keywords: ATP-binding cassette sub-family G member 2 (ABCG2); rs2231142; metastatic renal cell carcinoma (mRCC); sunitinib; toxicity

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Introduction

Renal cell cancer (RCC) is a common cancer in the urinary system and accounts for nearly 2–3% of all malignancies (1). The estimated new cases in the United

States in 2017 is 63,990, and estimated death is 14,400 (2). Besides, approximately a third of RCC patients suffering nephrectomy will progress to metastases renal cell cancer (mRCC) within 5 years (3). However, mRCC has been

demonstrated to be insensitive to chemotherapy and hormone therapy (4,5). Additionally, immunotherapy (interleukin 2 and interferon, etc.) contributes limited effects to mRCC, and duration of action is transient (6).

With the exploration of molecular mechanisms of tumorigenesis and progression, targeted therapy came to prominence in the treatment of mRCC. Sunitinib, as a small-molecule receptor tyrosine kinase inhibitor (TKI), was approved by the Food and Drug Administration (FDA) in 2006. And it is now considered as a first-line therapy of mRCC (1) contributed by the direct anti-tumor and anti-angiogenic activity (7). Although sunitinib exposure increase the overall survival (OS), several common sunitinib-induced adverse events were frequently observed (8-11). A randomized, double-blind, phase 3 trial suggested that treatment discontinuations owing to adverse events occurred in 86 patients (28.1%) in the sunitinib group and 17 (5.6%) in the placebo group (12). Furthermore, studies have confirmed that single nucleotide polymorphisms (SNPs) might be associated with pharmacokinetics and pharmacodynamics of sunitinib, thus affecting the toxicity and efficacy to the patients. Moreover, it was observed that SNPs might have effects on progression-free survival (PFS) of mRCC (11,13) after sunitinib therapy. However, the conclusions were inconsistent and conflicting findings were observed (14).

The human ATP-binding cassette sub-family G member 2 (ABCG2) gene is located on chromosome 4q22 and encodes a 655 amino acid polypeptide (15). ABCG2 contains 6 transmembrane domains and an ATP-binding domain, and it acts as a half transporter member in the ABCG subfamily (16). From a perspective of tissue distribution, studies have shown that ABCG2 is over-expressed in human placenta, small intestine, colon, and the bile canalicular membrane (17). The specific localization of ABCG2 suggested that it might regulate intestinal absorption and biliary secretion of potentially toxic xenobiotics through active transport mechanisms (18,19). Moreover, investigations have reported that ABCG2 could mediate the efflux of various anti-cancer drugs, including sunitinib (20) and relevant sunitinib-induced toxicity (9). However, some researchers held opposite opinions (9,10). Accordingly, we performed such systematic review for more precise results and more comprehensive understanding of association between rs2231142 and sunitinib-induced

toxicity.

Methods

Search strategy

We performed a systematic literature search based on the 'PRISMA' guideline (21). A systematic search on PubMed, EMBASE and Web of Science was performed to identify all potentially appropriate studies (till March 31st, 2017). The following key words were utilized ("genetic polymorphism", "SNP", or "single nucleotide polymorphism"), ("metastases renal cell carcinoma", "tumor", or "cancer"), and ("rs2231142", "ABCG2" and "ATP-binding cassette sub-family G member 2"). Additional publications were manually identified when we searched the reference lists of original articles. A flow diagram of the study selection process is presented in *Figure 1*.

Inclusion criteria and exclusion criteria

We filtered the articles with the following inclusion criteria: (I) studies estimating the associations between rs2231142 and sunitinib-induced toxicity in mRcc; (II) data involved in different studies were not overlapping. Conversely, the exclusion criteria were exhibited as follows: (I) Studies consisted no usable data of sunitinib-induced toxicity in mRCC; (II) studies had overlapped data.

Data extraction

All useful information involved in eligible studies were extracted by two investigators (YZ and CZ) independently. The review of results was carried out by a third investigator (CM). Name of first author, year of publication, ethnicity, number of patients, basic information of total patients, sunitinib-induced toxicity and Eastern Cooperative Oncology Group (ECOG) score were extracted for each selected study. Besides, relevant data of association between rs2231142 and sunitinib-induced toxicity was extracted from multivariate logistic regression analysis in 6 enrolled studies. The selected adverse effects were thrombocytopenia, neutropenia, hand-foot syndrome, any toxicity higher than grade 2, diarrhea, fever, hypertension, hypothyroidism, leucopenia and proteinuria. Furthermore, Newcastle-Ottawa Scale was performed to evaluate the

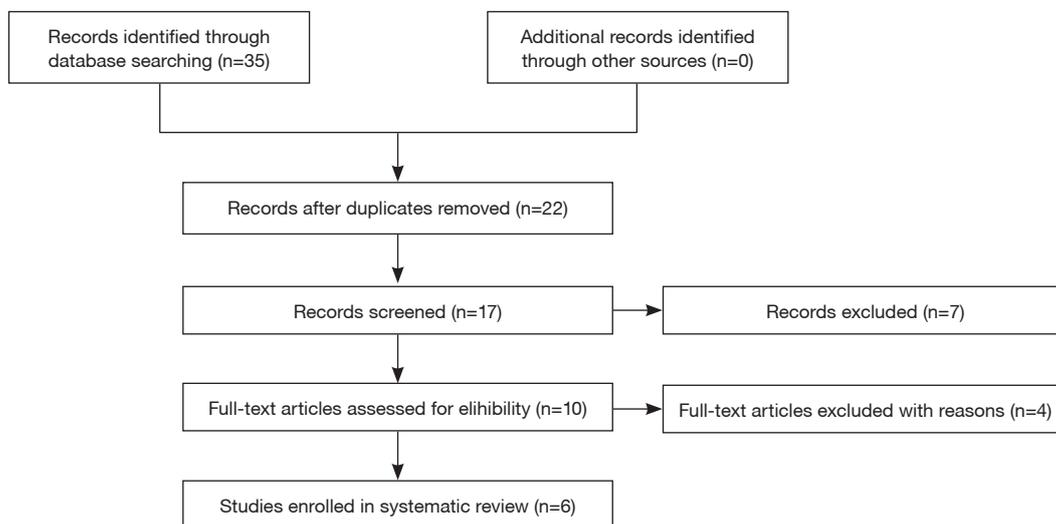


Figure 1 Flow chart of evidence search and selection.

quality of all studies enrolled in our study.

Results

Six relevant studies (9-11,14,22,23) were finally included in our review (*Table 1*). A total of 698 patients (495 male, 203 female) with an average age of 61.31 years old (18–87 years old) were included. Among these studies, the white were mainly studied in 2 articles, and they accounted for more than 90% of the total enrolled patients. Other 4 studies mainly contained Asian patients. In addition, the detailed information of weight (2 studies) and BSA (4 studies) were shown in *Table 1*. Besides, 2 studies reported the RCC histology, and 5 reported ECOG score of patients. Newcastle-Ottawa Scale of each studies enrolled in our study were shown in *Table 1*.

In articles enrolled our study, the treatment plan (dose and schedule) for sunitinib was 50 mg each day given orally for 4 consecutive weeks followed by 2 weeks-off per treatment cycle. Data about toxicity of sunitinib extracted from enrolled studies was recorded during the first treatment cycle. Sunitinib toxicity was assessed with the National Cancer Institute-Common Toxicity Criteria for Adverse Effects (NCI-CTCAE) version 3.0. Afterwards, the results of association between rs2231142 and sunitinib-induced toxicity was summarized in *Table 2*. Studies from Kim and Low reported ABCG2 AA was related to thrombocytopenia ($P=0.04$, $P<0.01$, respectively). However, van Erp *et al.* suggested that rs2231142 was not associated with thrombocytopenia ($P=0.12$, respectively). Furthermore,

rs2231142 was connected with neutropenia according to the results from the investigation of Kim and Chu ($P=0.02$, $P=0.03$, respectively), but the connection was not observed in Low's study ($P=0.37$). Articles from Kim and Garcia-Donas revealed rs2231142 had considerable association with hand-foot syndrome ($P=0.01$, $P=0.04$, respectively). On the contrary, the consequence was not shown in Low's study ($P=0.37$). Kim investigated that rs2231142 was related to any hematologic toxicity > grade 2 ($P=0.05$). In addition, research from Low suggested that rs2231142 was connected to fever ($P=0.02$), but not relevant with diarrhea ($P=0.31$), hypertension ($P=0.46$), hypothyroidism ($P=0.15$), leucopenia ($P=0.28$) or proteinuria ($P=0.21$).

Discussion

Sunitinib is a multitargeted TKI for the treatment of mRCC. Following administration, sunitinib is primarily metabolized by cytochrome P450 3A4 to an active N-desethyl metabolite (SU12262) (24). In addition, ABCB2 plays a role of a half transporter of sunitinib, and acts as a homodimeric/oligomeric efflux pump (25). For this reason, the expression level of ABCG2 affects the metabolic of sunitinib, which leads to affects the exposure of sunitinib in vivo. For example, a study reported that brain accumulation of sunitinib was markedly (23-fold) increased in ABCB1-ABCG2 co-knockout mice, but only slightly (2.3-fold) in ABCB1 knockout mice (26). Thus, the exposure of sunitinib but not the dose should be the first condition to consider when we explore the toxicities caused by sunitinib. A meta-

Table 1 Main characteristics of studies involved in this systematic review

First author	Year	Ethnicity	No. of patients	Sex		Age# (years)	Weight*	BSA*	mRCC Histology			ECOG score			NOS			
				Male	Female				CCC	Other	Unknown	0	1	2		3	M	
Garcia-Donas	2011	White	95	65	30	65 [42-87]	NA	NA	NA	NA	NA	25	56	8	0	6	6	
Kim	2013	Asian	65	51	14	59 [36-81]	65.3±0.03	1.7±0.1	61	3	1	18	37	8	1	NA	6	
Chu	2015	Asian	97	75	22	58 [18-79]	NA	1.63 [1.18-1.92]	NA	NA	N	27	51	13	6	NA	7	
Low	2016	Asian	219	161	58	63 [32-83]	NA	NA	176	30	13	159	45	11	2	2	7	
Mizuno	2012	Asian	19	14	5	62 [21-79]	58 [44-78]	1.59 [1.31-1.81]	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
van Erp	2009	White	203	129	74	60 [20-84]	NA	1.93 [1.47-2.51]	NA	NA	NA	81	90	17	8	7	7	

#, median age at time of sunitinib treatment [range]; *, mean ± SD or median [range]. CCC, clear cell carcinoma; mRCC, metastatic renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; M, missing; NA, not available; NOS, Newcastle-Ottawa Scale.

analysis enrolled 14 studies with 590 subjects suggested that increased exposure to sunitinib and/or SU12662, which may in turn increase the incidence or severity of adverse events (8).

Three variant ABCG2 cDNAs harboring the following substitutions: 34G > A (V12M), 421C > A (Q141K) and an amino acid deletion of residues 944-949 that lacks Ala-315 and Thr-316 (Δ315-6) (27). Besides, study suggested that rs2231142 ABCG2-transfected murine fibroblast PA317 (PA/Q141K) cells display lower exogenous ABCG2 protein levels than the wild-type ABCG2-transfected cells. Furthermore, in PA317 cells, intracellular topotecan accumulation was higher compared with other ABCG2 transfectants, showing rs2231142 might influence ABCG2 function (27). Additionally, rs2231142 was demonstrated to locate within the ATP-binding region between the Walker A and B motifs of ABCG2, and this polymorphism could regulate the activity of ATPase, which led to affect the biochemical process of cells (28,29). In summary, rs2231142 may affect the activity of ABCG2 as a sunitinib transport pump by altering the activity of intracellular ATPase and/or regulate the ABCB2 protein level, which allows sunitinib to accumulate in cells and the level of sunitinib exposure after administration, and enhance sunitinib-induced toxicity.

In our study, we found that rs2231142 may associated with sunitinib-induced toxicity such as thrombocytopenia, neutropenia, hand-foot syndrome, fever and any hematologic toxicity (> grade 2). However, the connections between rs2231142 and diarrhea, hypertension, hypothyroidism, leucopenia, proteinuria were not observed in our review.

Reports indicated that ABCG2 rs2231142 appeared to be a very common ABCG2 polymorphism in Asian populations, and the reported allelic frequencies were 27-34% (27,29,30). However, the frequency was approximately 10% in white populations, and less than 5% in sub-Sahara African and in African-American. Differences in SNP distribution among races may lead to the discrepancy of sunitinib-induced toxicity incidence in patients with different ethnicity. In our review, the adverse effects after sunitinib was mainly observed in studies enrolled Asian patients. However, several conflict results were exhibited in different Asian studies. To reduce the false positive rate, high-quality studies with large amount of samples are still needed, whether they are based on Asian populations or other races.

Limitations also existed in our review. First, we only enrolled 6 articles which focused on the association between rs2231142 and sunitinib-induced toxicity in mRCC. With a growing number of high-quality studies being published, more capable studies will be enrolled and summarized

Table 2 Summary results of the association between rs2231142 and sunitinib-induced toxicity in mRCC

Sunitinib-induced toxicities	Genotype	OR	95% CI	P value	First author
Thrombocytopenia	CC + CA; AA	9.9	(1.16–infinity)	0.04	Hye Ryun Kim
	CC; CA + AA	1.93	(0.85–4.42)	0.118	Nielka P. van Erp
	CC + CA; AA	1.856	(1.172–2.939)	0.000841	Siew-Kee Low
Neutropenia	CC + CA; AA	18.2	(1.49–222.09)	0.02	Hye Ryun Kim
	CC + CA; AA	0.3	(0.1–0.9)	0.03	Ying-Hsia Chu
	CC + CA; AA	0.856	(0.512–1.431)	0.553	Siew-Kee Low
Hand-foot syndrome	CC + CA; AA	28.46	(2.22–364.94)	0.01	Hye Ryun Kim
	CC + CA; AA	1.24	(0.78–1.98)	0.369	Siew-Kee Low
	CC + CA; AA	0.11 (HR)	(0.01–0.92)	0.04	Jesus Garcia-Donas
Any hematologic toxicity > grade 2	CC + CA; AA	8.24	(0.99–infinity)	0.05	Hye Ryun Kim
Diarrhea	CC + CA; AA	1.468	(0.703–3.067)	0.307	Siew-Kee Low
Fever	CC + CA; AA	2.845	(1.216–6.657)	0.0159	Siew-Kee Low
Hypertension	CC + CA; AA	1.23	(0.713–2.724)	0.457	Siew-Kee Low
Hypothyroidism	CC + CA; AA	1.402	(0.89–2.208)	0.145	Siew-Kee Low
Leucopenia	CC + CA; AA	0.712	(0.385–1.316)	0.278	Siew-Kee Low
Proteinuria	CC + CA; AA	1.456	(0.806–2.631)	0.213	Siew-Kee Low

mRCC, metastatic renal cell carcinoma; OR, odds ratio; CI, confidence interval.

in the future. Second, our systematic review was based on individual articles with different contents, which may reduce the representation of the final results. Third, more indicators about sunitinib-induced toxicity have yet to be further explored, and further confirmation with long term results were required.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2017.05.24>). Dr. Li serves as an unpaid section editor of *AME Medical Journal*. The other authors have no conflicts of interest to declare.

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appropriately investigated and resolved.

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