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REVIEW ARTICLE

Genetic polymorphisms associated with adverse reactions of molecular targeted therapies in renal cell carcinoma

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Abstract

The prognosis of patients with metastatic renal cell carcinoma has drastically improved due to the development of molecular targeted drugs and their use in clinical practice. However, these drugs cause some diverse adverse reactions in patients, and sometimes affect clinical outcomes of cancer therapy. Therefore, predictive markers are necessary to avoid severe adverse reactions, to establish novel and effective prevention methods, and to improve treatment outcomes. Some genetic factors involved in these adverse reactions have been reported; however, perspectives on each adverse response have not been integrated yet. In this review, genetic polymorphisms relating to molecular targeted therapy-induced adverse reactions in patients with renal cell carcinoma are summarized in the points of pharmacokinetic and pharmacodynamic mechanisms. We also discuss about the relationship between systemic drug exposure and adverse drug reactions.

Keywords

adverse drug reaction, molecular targeted drug, polymorphism, renal cell carcinoma, pharmacokinetics, pharmacodynamics

Introduction

A number of novel drugs based on molecular targets relating to the progression of renal cell carcinoma (RCC) have been developed and used in clinical practice, drastically improving the prognosis of patients with metastatic RCC [1, 2]. However, specific adverse reactions which are not popular in the treatment with ordinal cytotoxic cancerous drugs are being reported [3-5]. A crucial issue in the safe and effective targeted chemotherapy is to identify mechanisms and predictive markers of adverse drug reactions.

Some genetic factors of adverse drug reactions have been reported and broadly classified into pharmacokinetic and pharmacodynamics mechanisms. A part of molecular targeted drugs are absorbed and distributed by various membrane transporters such as ATP-binding cassette (ABC) and solute carrier (SLC) transporters [6]. Moreover, almost all of these drugs are metabolized by cytochrome P-450s (CYPs). A large number of polymorphisms exist in the coding genes of factors involved in absorption, distribution, metabolism, and excretion (ADME) processes; these polymorphisms can affect the systemic and local concentrations of the drugs [7]. Polymorphisms in drug-targeted molecules such as vascular endothelial growth factor receptor (VEGFR) and FMS-like tyrosine kinase (FLT) 3 are associated with the efficacy and toxicity of the drugs [8]. Various reports on individual adverse reactions can be found; however, different perspectives on adverse responses have not been integrated yet, which is

necessary for the development of preventive strategies against these adverse drug reactions and for their optimal usage in drug selection or dosage adjustment in clinical practice.

In this review, genetic factors relating to molecular targeted therapy-induced adverse drug reactions in patients with RCC are summarized based on pharmacokinetic and pharmacodynamic mechanisms.

TKI-induced adverse reactions

Clinically, tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin inhibitors (mTORi), and immune checkpoint inhibitors are used in RCC therapy. Several TKIs have been in use based on patient performance status; novel TKIs will continue to be developed [9, 10]. Molecular targeted therapy-induced major adverse reactions recorded in leading clinical trials that evaluated the efficacy of first-line RCC therapy are shown in Table 1 [11-16]. Gastrointestinal toxicities such as diarrhea and fatigue are common reactions to TKIs. In addition, skin or mucosal toxicities such as hand–foot skin reaction, rash, and stomatitis are typical. Racial differences in the development of hand–foot skin reaction have been reported [17]. Liver injury is frequently induced by sunitinib and pazopanib. Hematological toxicities such as anemia, neutropenia, and thrombocytopenia are commonly observed events in sunitinib and pazopanib therapy; particularly sunitinib-induced hematological toxicity is likely to

68 become severe, whereas sorafenib and axitinib are known to be less hematotoxic than
69 other TKIs. Proteinuria and hypothyroidism are unique events in axitinib therapy.
70 Interestingly, some reactions are well-known to be associated with the efficacy of TKI
71 cancer therapy [18, 19].
72
73 **mTORi-induced adverse reactions**
74 Oral everolimus and intravenous temsirolimus are mTORi used for the therapy of
75 RCC. mTORi-induced adverse reactions differ from TKI-induced adverse reactions.
76 Mucositis such as stomatitis is more frequently observed in the mTORi therapy. Skin
77 disorders such as dry skin and paronychia are also reactions unique to these inhibitors.
78 In addition, interstitial lung disease (ILD) is a critical reaction, and it is the key factor in
79 the interruption of mTORi therapy, although its development is rare [20]. Racial
80 differences in the development of ILD have been reported, with Asian patients being
81 more likely to experience mTORi-induced ILD [21, 22]. Another unique adverse
82 reaction to mTORi therapy is abnormality in lipid and glucose metabolism, which is
83 known to occur at different frequencies comparing everolimus and temsirolimus therapy.
84 Some mTORi-induced adverse reactions are also associated with therapeutic outcome
85 [23-25].
86
87 **Genetic factors associated with adverse reactions**

TKI-induced diarrhea

Diarrhea is the most common adverse response to TKIs. Reported genetic polymorphisms are related with their pharmacokinetic mechanisms (Table 2). In a retrospective study, Chu *et al*. reported that the T allele of 1236 T/C (rs1128503) and that of 3435 T/C (rs1045642) in the *ABCB1* gene reduced the risk of sunitinib-induced diarrhea in Chinese patients as secondary endpoints [26]. The TT genotype of 1236 T/C and that of 2677 G/T (rs2032582) in the *ABCB1* gene are known to increase the clearance of sunitinib and its active metabolite [27]. In addition, Boudou-Rouquette *et al*. emphasized that the T allele of -2152 C/T (rs17868320) in the UDP-glucuronosyltransferase (*UGT*) *1A9* gene is associated with sorafenib-induced diarrhea, because this SNP is related with the higher hepatic expression of UGT1A9 and can increase the glucuronidation activity [28]. Further, Bins *et al*. reported the association between the G allele of 388 A/G (rs2306283) in the *SLCO1B1* gene and development of sorafenib-induced diarrhea [29]. Suttle *et al*. reported that pazopanib-induced diarrhea showed a tendency of correlation with area under the curve (AUC) of pazopanib [30]. On the other hand, no reports about the association between the development of TKI-induced diarrhea and pharmacodynamic factors based on genetic information can be found. Therefore, these findings suggested that TKI-induced diarrhea was associated with the activity or expression of transporters and conjugation enzymes affecting drug systemic exposure and distribution to local tissues. TKI-induced

diarrhea can largely be explained by the genetic polymorphisms in the pharmacokinetic mechanisms.

TKI-induced hand–foot skin reaction

Several previous reports showed that hand–foot skin reaction was related to genetic polymorphisms of both pharmacokinetic and pharmacodynamics mechanisms. The TTT haplotype of rs1045642, rs1128503, and rs2032582 in the *ABCB1* gene was associated with the development of hand–foot skin reaction due to increased systemic exposure [31, 32]. In addition, it was reported that carriers of the AA genotype of 421 C/A (rs2231142) in the *ABCG2* gene developed hand–foot skin reaction more frequently. In this report, higher systemic exposure because of lower expression of breast cancer resistant protein (BCRP) with occurrence of the A allele of rs2231142 in the *ABCG2* gene was a significant cause of frequent hand–foot skin reaction [33]. On one hand, an association between systemic exposure to sunitinib and development of hand–foot skin reaction is controversial. Mizuno *et al*. showed the lack of association between AUC of sunitinib and development of hand–foot skin reaction in secondary evaluations in a small-sample study [34]. Noda *et al*. also reported no significant association between severity of hand–foot skin reaction and plasma trough concentration of sunitinib and its metabolite [35]. However, some studies have found that sorafenib concentrations were significantly correlated to the grade of hand–foot skin reaction [36, 37]. Genetic variants

128 of the *UGT1A9* gene were found to be associated with AUC of sorafenib and grade of
129 hand–foot skin reaction [38, 39, 37, 28]. The severity of pazopanib-induced hand–foot
130 skin reaction was also correlated to AUC of pazopanib [30]. Therefore, sorafenib- or
131 pazopanib-induced hand–foot skin reaction may be associated with their systemic
132 exposure of these drugs, and genetic variants of transporters may affect the local
133 accumulation of TKIs.

134 A few factors in pharmacodynamic mechanisms of hand–foot skin reaction have
135 been reported. Several reports focused on VEGF, VEGFR, and FLT3, which are targets
136 of TKIs [40-42]. Mutations in the 5' UTR or 3' UTR such as rs2010963 in the *VEGF*
137 gene can modify the potential binding sites of transcription factors, resulting in lower
138 expressions of VEGF [43, 44]. Moreover, because 1192 G/A (rs2305948) and 1719 A/T
139 (rs1870377) in the *VEGFR2* gene affect the VEGF binding domain, these
140 polymorphisms may have a differential effect on VEGF ligand binding and its
141 downstream signaling through VEGFR2 [45]. Overall, patients with weaker signaling in
142 the VEGF/kinase insert domain–containing receptor (KDR) pathway may more
143 frequently develop hand–foot skin reaction; however, further information is needed for
144 confirmation.

145 An association between development of hand–foot skin reaction and SNPs in
146 cytokine-related factors such as tumor necrosis factor (TNF)-α and signal transducer
147 and activator of transcription (STAT) 3 has been recently suggested [46, 38]; thus,

148 indirect factors may contribute to the mechanism of hand–foot skin reaction. Therefore,
149 hand–foot skin reaction is likely to involve integrated mechanisms including
150 pharmacokinetic, pharmacodynamic, and indirect factors.
151
152 *Sorafenib-induced skin rash*
153 Skin rash is an adverse reaction involving immunological mechanisms, unlike
154 hand–foot skin reaction. An association between sorafenib-induced skin rash and human
155 leukocyte antigen (*HLA)-A**24 has been reported in a small Japanese population.
156 *HLA-A**24 is known to be associated with phenytoin and lamotrigine-induced Stevens–
157 Johnson syndrome (SJS) or toxic epidermal necrolysis; this can be relevant to allergic
158 responses induced by different drugs. On the other hand, Tsuchiya *et al*. reported that
159 patients with the CC genotype of -24 C/T (rs717620) in the *ABCC2* gene were at a
160 significantly higher risk of skin rash than those with the CT genotype [47]. Carriers of
161 the C allele of −24 C/T in the *ABCC2* gene show a higher export function of the
162 multidrug resistance-associated protein 2 (MRP-2) than carriers of the T allele [48, 49].
163 Therefore, patients with C allele may experience lower plasma concentrations of
164 sorafenib, because MRP-2 mediates the biliary excretion of sorafenib [50]. On one hand,
165 Fukudo *et al*. reported a lack of association between sorafenib plasma concentration and
166 severe (> grade 2) skin rash. Relationship between pharmacokinetic factors and
167 sorafenib-induced skin rash remained to be examined further.

168

169 *Sunitinib-induced mucositis*

170 Some reports investigated about the pharmacokinetic mechanisms in
171 sunitinib-induced stomatitis. Diekstra *et al*. reported the associations between
172 development of stomatitis and SNPs in *ABCB1;* they also reported that ligand-activated
173 nuclear receptor (*NR*)*1/3* genes affect the expression of CYP3A4 [51, 41]. Interestingly,
174 polymorphisms in the *ABCB1* gene influence the concentration of P-glycoprotein
175 substrates in saliva [52]. Therefore, TKI-induced stomatitis can be related to the drug
176 concentration in the oral cavity, but not to the systemic concentration. It is also reported
177 that SNPs in *NR1/3* and *CYP1A1* genes are associated with the development of
178 stomatitis [41, 31]. Carriers of the G allele of 4889 A/G (rs1048493) in the *CYP1A1*
179 gene have a higher catalytic activity of CYP1A1 [53, 54]. An association between
180 systemic plasma concentration and development of sunitinib-induced stomatitis is
181 generally accepted.

182 Watanabe *et al*. reported that sunitinib-induced stomatitis more frequently
183 develops in carriers of STAT3 genetic polymorphisms [55]. TKI-induced mucositis may
184 be related to immune system function; however, further studies are required for
185 confirmation.

186

187 *TKI-induced hypertension*

188 Sunitinib-induced hypertension is reported to be associated with 6986 A/G
189 (rs776746) in the *CYP3A5* gene and rs2231142 in the *ABCG2* gene, and these SNPs
190 affect the systemic concentration of sunitinib [41]. Moreover, sorafenib-induced
191 hypertension is reported to be associated with rs1045642 in the *ABCB1* gene [42]. It has
192 been suggested that rs776746 in the *CYP3A5* gene can be a dose reduction marker of
193 sunitinib, because rs776746 A allele carriers have higher concentrations of sunitinib
194 [56]. Furthermore, carriers of the *ABCG2* rs2231142 AA genotype have higher AUC of
195 substrate drugs than carriers of the CC genotype [57, 58]. In addition, rs4646437 G/A in
196 the *CYP3A4* gene was reported to be associated with sunitinib-induced hypertension
197 [59]. The A allele of rs4646437 is associated with a high plasma concentration of
198 substrate drugs [60] due to altered splicing of primary transcripts [61]. Therefore,
199 carriers of the rs4646437 A allele have increased drug exposure with stronger inhibition
200 of VEGFR in patients taking sunitinib [59]. An association between TKI-induced
201 hypertension and high systemic exposure to TKI has been reported [34, 62, 37].
202 Polymorphisms related to the VEGF/KDR pathway are also associated with
203 TKI-induced hypertension [63, 40]. It is considered that these SNP carriers have
204 reduced signaling in the VEGF/KDR pathway. Moreover, Diekstra *et al*. also reported
205 an association between hypertension and polymorphisms in the *IL-8* gene [64]. The
206 effect of SNPs in the *IL8* gene is little known; however, these SNPs are expected to
207 affect the protein expression of IL8 [65-67]. It also remains unclear how the IL8 protein

may relate to sunitinib-induced hypertension; IL8 may directly or indirectly influence the VEGFR pathway [68, 69].

TKI-induced liver injury

Pazopanib-induced hyperbilirubinemia was associated with *UGT1A1**28 (rs8175347) [70, 29]. Bilirubin is metabolized by UGT1A1 for the biliary elimination, and UGT1A1 activity is strongly inhibited by pazopanib. Because the UGT1A1 genetic variant TA7 is known to cause reduced expression of UGT1A1 [71], its carriers may be susceptible to the inhibitory effects of pazopanib. This UGT1A1 TA-repeat polymorphism has also been reported to associate with hyperbilirubinemia induced by several drugs [72-74]. Low *et al*. reported that the *ABCG2* rs2231142 variant was associated with sunitinib-induced hepatic transaminase (AST and ALT) increase [75]. In addition, some studies found that plasma concentrations of sorafenib or pazopanib show a tendency of correlation with ALT increase [30, 37]. Interestingly, Xu *et al*. reported that the rs2858996/rs707889 polymorphisms in the *HFE* gene may associate with the reversible ALT elevation in pazopanib-treated patients [76]. *HFE*, the hemochromatosis gene, encodes a membrane protein that regulates iron homeostasis. Genetic mutations in this gene result in hereditary hemochromatosis, an iron storage disorder. Other HFE-associated syndromes such as nonalcoholic steatohepatitis result in liver injury because of aberrant iron metabolism and oxidative stress [77, 78]. Furthermore, HFE

and VEGFR-2 share several hypoxia-induced transcriptional regulators, particularly hypoxia inducible factor (HIF)-1α; the inhibition of VEGF signaling may reduce induction of HFE [79]. Xu *et al*. also reported that *HLA*-B057:01 confers higher risk of ALT elevation in patients receiving pazopanib [80]. Recent pharmacogenetic studies of hepatotoxicity have identified strong associations between *HLA* polymorphisms and various drug-induced ALT elevations [81-85].

Liver injury is a complex condition that cannot be justified by individual mechanisms. Hyperbilirubinemia may be related to pharmacokinetic differences in bilirubin metabolism inhibition by TKIs between *UGT1A1* genetic variant carriers; ALT elevation may be associated with the factors in pharmacokinetic and pharmacodymic mechanisms including immune components such as HLA and iron storage homeostasis.

TKI-induced thrombocytopenia

Some reports have suggested that TKI-induced thrombocytopenia is associated with pharmacokinetic factors. Studies have shown an association between sunitinib-induced thrombocytopenia and rs2231142 in the *ABCG2* gene in Japanese and Korean patients [75, 33]. Carriers of the *ABCG2* rs2231142 C allele are known to have higher AUC of sunitinib [34]. In addition, studies have suggested associations between plasma trough level of sunitinib and platelet counts, and between AUC of sunitinib and development of thrombocytopenia [34, 35]. Therefore, TKI-induced thrombocytopenia

248 may be a hematological toxicity dependent on systemic drug exposure. Moreover, Bins
249 *et al*. showed an association between 521 C/T (rs4149056) in the *SLCO1B1* gene and
250 sorafenib-induced thrombocytopenia [29]. Some TKIs including nilotinib, pazopanib,
251 sorafenib, and sunitinib are substrates of OATP1B1 encoded by the *SLCO1B1* gene [86,
252 87] with rs4149056 T allele carriers showing higher concentration of the substrates [88].
253 These findings support the hypothesis that TKI-induced thrombocytopenia is dependent
254 on systemic drug exposure.
255
256 *Sunitinib-induced leukopenia*
257 Leukopenia is a type of hematological toxicity; therefore, the occurrence of
258 leukopenia is considered to associate with systemic concentration of TKIs. However,
259 some factors in pharmacodynamic mechanism are also reported. van Erp *et al*. reported
260 that sunitinib-induced leukopenia is associated with rs1048943 in the *CYP1A1* gene and
261 the CAG haplotype (rs2307424, rs2307418, and rs4073054) in the *NR1/3* gene, but not
262 with SNPs in the VEGFR genes [31].
263 Sunitinib is likely to be a substrate of CYP1A1 and is known to be an inducer of
264 CYP1A1 protein mediated by aryl hydrocarbon receptor activation [89, 90]. Lu *et al*.
265 found that Caucasians with the rs1048943 GG genotype in the *CYP1A1* gene might
266 have an increased risk of acute lymphoid leukemia and chronic myelogenous leukemia
267 [91, 92]. This SNP results in increased catalytic activity and higher mRNA level of

268 CYP1A1, leading to enhanced DNA adduct formation [93]. These DNA adducts are
269 responsible for causing mutations in tumor suppressor genes and oncogenes; thus,
270 trigger uncontrolled hematopoietic cell proliferation and reduced differentiation and
271 decreased apoptosis of malignant hematopoietic blast cells [54]. It is not yet clear if
272 these mechanisms are associated with sunitinib-induced leukopenia; however, *CYP1A1*
273 variants may be a factor of pharmacodunamic mechanism if the above mechanism
274 involves sunitinib-induced leukopenia. NR1/3 is well known to regulate the expression
275 of CYP3A4. Although the CAG haplotype in the *NR1/3* gene is likely to lead to a higher
276 concentration of sunitinib [94], this mechanism remains to be clarified.
277 Some studies have found that sunitinib-induced leukopenia is associated with
278 *FLT3* variants [26, 31]. The importance of the FLT3 receptor has been described with
279 respect to the development of several subtypes of leukemia, wherein *FLT3* is frequently
280 overexpressed and/or mutated [95, 96]. The functional effect of 738 C/T (rs1933437) in
281 the *FLT3* gene is not yet clarified; however, its protein product may be altered because
282 of amino acid substitution.
283
284 *mTORi-induced adverse reactions*
285 Associations between mTORi-induced adverse reactions in RCC therapy and
286 genetic polymorphisms related to pharmacokinetic or pharmacodynamic factors are yet
287 to be elucidated. However, the association between everolimus-induced adverse

288 reactions in patients with breast cancer and genetic polymorphisms was reported [97]. It
289 is reported that polymorphisms in mTOR pathway-related factors are associated with
290 everolimus-induced leucopenia, hyperglycemia, and pneumonitis; however, data in
291 patients with RCC has not been reported. de Velasco *et al*. reported a lack of association
292 between adverse reactions to everolimus or temsirolimus and some genetic
293 polymorphisms such as *CYP3A4*, *CYP3A5*, and *ABCB1* [98]. de Wit *et al*. found that
294 patients with everolimus-induced severe stomatitis (grade 3) had higher AUC and
295 trough concentration than patients with non-severe stomatitis (grade 0–2); however, the
296 development of stomatitis (any grade) was not associated with AUC or trough
297 concentration. Thus, mTORi-induced adverse reactions may be not influenced by
298 pharmacokinetic genetic factors.
299
300 *Conclusion and perspectives*
301 Understanding the mechanism of adverse reactions and identifying genetic
302 markers have become increasingly important because of spiraling medical costs and
303 development of different molecular-targeted drugs. The application of genetic
304 engineering techniques to medical research, such as genome-wide association studies, is
305 showing good progress. Therefore, mechanistic analysis of targeted therapy based on
306 genetic information is also necessary. Although a lot of retrospective or secondary
307 analytic data have accumulated, there continues to be a lack of reports evaluating

clinical outcome by using genetic information while controlling or avoiding adverse reactions in prospective studies. This review is aimed at encouraging the practical use of genetic information for the management of molecular targeted drug-induced adverse drug reactions.

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Compliance with ethical standards

Conflict of interest

The authors declared no conflicts of interest.

Human and animal rights

This article does not contain any studies with human participants or animals performed by the authors.

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685

Table 1 Major adverse reactions induced by molecular targeted therapy in patients with RCC

Drug	Adverse reaction (≥20%)	Any grade (%)	Grade ≥3 (%)	Laboratory abnormality (≥20%)	Any grade (%)	Grade ≥3 (%)	N	Reference (Ethnicity)
Sorafenib	Diarrhea	43	2	None			451	Escudier *et al*. 2007 [11]
	Rash	40	1					(Non-information)
	Fatigue	37	5					
	Hand-foot skin reaction	30	6					
	Alopecia	27	<1					
	Nausea	23	<1					
Sunitinib	Diarrhea	61	9	Anemia	79	8	375	Motzer *et al*. 2009 [12]
	Fatigue	54	11	Leukopenia	78	8		(Non-information)
	Nausea	52	5	Neutropenia	77	18		
	Dysgeusia	46	<1	Increased creatinine	70	<1		
	Anorexia	34	2	Thrombocytopenia	68	9		
	Dyspepsia	31	2	Lymphocytopenia	68	18		
	Vomiting	31	4	Increased lipase	56	18		
	Hypertension	30	12	Increased AST/ALT	56 (AST)	2		
	Stomatitis	30	1	Increased creatine kinase	49	3		
	Hand-foot syndrome	29	9	Increased ALP	46	2		
	Skin discoloration	27	<1	Increased uric acid	46	14		
	Mucosal inflammation	26	2	Increased amylase	35	6		
	Rash	24	1	Hypophosphatemia	31	6		
	Dry skin	21	<1	Increased total bilirubin	20	1		
	Asthenia	20	7					
	Hair color changes	20	0					
Axitinib	Diarrhea	50	9	Hypothyroidism	21	0	189	Hutson *et al*. 2013 [13]
	Hypertension	49	14					(White: 71)
	Weight decrease	37	8					(Black: <1)
	Fatigue	33	5					(Asian: 25)
	Decreased appetite	29	2					(Others: 4)
	Palmar-plantar Erythrodysaesthesia	26	7					
	Dysphonia	23	1					
	Asthenia	21	8					
	Nausea	20	1					
Pazopanib	Diarrhea	52	4	Increased AST/ALT	53	12 (ALT)	290	Sternberg *et al*. 2010 [14]
	Hypertension	40	4	Hyperglycemia	41	<1		(White: 87)
	Hair color changes	38	<1	Leukopenia	37	0		(Black: <1)
	Nausea	26	<1	Increased total bilirubin	36	3		(Asian: 12)
	Anorexia	22	2	Neutropenia	34	1		(Other: <1)
	Vomiting	21	2	Hypophosphatemia	34	4		
				Hypocalcemia	33	3		
				Thrombocytopenia	32	1		
				Lymphocytopenia	31	4		
				Hyponatremia	31	5		
Everolimus	Stomatitis	40	3	Anemia	91	9	269	Motzer *et al*. 2008 [15]
	Rash	25	<1	Hypercholesterolaemia	76	3		(Non-information)
	Fatigue	20	3	Hypertriglyceridaemia	71	<1		
				Hyperglycaemia	50	12		
				Increased creatinine	46	<1		
				Lymphopenia	42	15		
				Increased ALP	37	<1		
				Hypophosphataemia	32	4		
				Leukopenia	26	0		
				Increased AST	21	<1		
				Thrombocytopenia	20	<1		
Temsirolimus	Asthenia	51	11	Anemia	45	20	208	Hudes *et al*. 2007 [16]
	Rash	47	4	Hyperlipidemia	27	3		(Non-information)
	Nausea	37	2	Hyperglycemia	26	11		
	Anorexia	32	3	Hypercholesterolemia	24	1		
	Pain	28	5					
	Dyspnea	28	9					
	Infection	27	5					
	Diarrhea	27	1					
	Peripheral edema	27	2					
	Cough	26	1					
	Fever	24	1					
	Abdominalpain	21	4					
	Stomatitis	20	1					
	Constipation	20	0					
	Back pain	20	3					

Table 2. Association of genetic polymorphisms and toxicities induced by molecular targeted drugs depending on pharmacokinetic and pharmacodynamic mechanisms

Toxicity	Phamacokinetic mechanisms							Pharmacodynamic mechanisms					
	Drug	Reference	Ethnicity	Sample size	Gene name	Associated SNP	OR/HR [95%CI]	Reference	Ethnicity	Sample size	Gene name	Associated SNP	OR/HR [95%CI]
Diarrhea	Sunitinib	Chu *et al.* 2015	Chinese 89%	97 (RCC)	*ABCB1*	rs1128503 rs1045642	0.04 [0.0–0.2] 0.3 [0.1–0.8]						
	Sorafenib	Boudou-Rouquette *et al.* 2012	Caucasian	54	*UGT1A9*	rs17868320	14.33 [1.46–140.50]						
		Bins *et al.* 2016	Caucasian	114 (HCC, RCC)	*SLCO1B1*	rs2306283	0.125 [0.025–0.64]						
Hand-foot skin reaction	Sunitinib	van Erp *et al.* 2009	Caucasian 93.6%	182 (mRCC, GIST, others)	*ABCB1*	rs1045642 rs1128503 rs2032582	0.39 [0.16–0.94]	Diekstra *et al.* 2015	Caucasian 96%	333 (mRCC)	*VEGFR2* *FLT3*	rs2305948 rs1933437	2.84 [1.09–7.38] 5.33 [1.10–25.79]
		Numakura *et al.* 2017	Japanese	70 (mRCC)	*ABCB1*	rs2032582	3.17 [1.06–9.52]	Yamamoto *et al.* 2016	Japanese	60 (mRCC) various TKI	*STAT3*	rs4796793	10.75 [2.38–48.07]
		Kim *et al.* 2013	Korean 100%	65 (mRCC)	*ABCG2*	rs2231142	28.46 [2.22–364.94]	Jain *et al.* 2010	Caucasian 82%	170 (Various tumors) (and/or bevacizumab)	*VEGFR2*	rs1870377	2.66 [1.28–5.52]
	Sorafenib	Lee *et al.* 2013	Korean	59 (HCC)	*UGT1A9*	rs7574296	18.72 [1.76–198.84]	Lee *et al.* 2013	Korean	59 (HCC)	*TNF-α* *VEGF*	rs1800629 (1991C>T)	44.06 [1.69–1149.91] 45.68 [2.41–865.03]
		Mai *et al.* 2017	Chinese	94 (mRCC)	*UGT1A9*	rs17868320		Qin *et al.* 2016	Chinese	100 (RCC)	*VEGFA*	rs2010963	10.32 [2.67–40.03]
Skin Rash	Sorafenib	Tsuchiya *et al.* 2013	Japanese	33 (RCC)	*ABCC2*	rs717620	N.A.	Tsuchiya *et al.* 2013	Japanese	33 (RCC)	*HLA*	A*24	N.A.
Mucositis	Sunitinib	van Erp *et al.* 2009	Caucasian 93.6%	193 (mRCC, GIST)	*CYP1A1*	rs1048943	4.03 [1.24–13.09]	Watanabe *et al.* 2017	Japanese	52 (mRCC)	*STAT3*	rs744166	6.91 [1.20–39.7]
		Diekstra *et al.* 2015	Caucasian 96%	333 (mRCC)	*ABCB1* *ABCB1* *NR1/3*	rs1128503 rs2032582 rs2307418	0.19 [0.04–0.83] 0.22 [0.05–0.98] 8.09 [1.55–42.3]						
Hypertension	Sunitinib	Diekstra *et al.* 2015	Caucasian 96%	333 (mRCC)	*CYP3A5* *ABCG2*	rs776746 rs2231142	4.70 [1.47–15.0] 0.03 [0.001–0.85]	Kim *et al.* 2012	Caucasian	63 (mRCC)	*VEGF*	rs699947 rs833061 rs2010963	N.A. N.A. N.A.
		Diekstra *et al.* 2017	Caucasian 97%	287 (mRCC)	*CYP3A4*	rs4646437	2.43 [1.14–5.18]	Diekstra *et al.* 2015	Caucasian 96%	372 (mRCC)	*IL-8*	rs1126647	1.69 [1.07–2.67]
	Sorafenib	Qin et al. 2016	Chinese	100 (RCC)	*ABCB1*	rs1045642	4.00 [1.09–14.67]	Jain *et al.* 2010	Caucasian 82%	170 (Various tumors) (and/or bevacizumab)	*VEGFR2*	rs1870377	2.34 [1.19–4.59]
Liver injury	Sunitinib	Low *et al.* 2016	Japanese	219 (RCC)	*ABCG2*	rs2231142	2.184 [1.03–4.64]						
	Sorafenib	Bins *et al.* 2016	Caucasian 91%	114 (HCC, RCC)	*UGT1A1* *SLCO1B1*	rs8175347 rs2306283	5.413 [1.36–21.51] 1.230 [1.10–1.37]						
	Pazopanib	Xu et al. 2010	Caucasian	236 (RCC)	*UGT1A1*	rs8175347	N.A.	Xu *et al.* 2011	Caucasian	242 (RCC)	*Hemochromatosis (HFE)*	rs2858996	N.A.
								Xu *et al.* 2016	Caucasian	2,190 (RCC, STS, ovarian)	*HLA-B057:01*	rs2395029 rs3093726	1.4 [1.2–1.6]
Thrombocytopenia	Sunitinib	Low *et al.* 2016	Japanese	219 (RCC)	*ABCG2*	rs2231142	1.856 [1.17–2.94]						
		Kim *et al.* 2013	Korean	65 (mRCC)	*ABCG2*	rs2231142	9.90 [1.16–infinity]						
	Sorafenib	Bins *et al.* 2016	Caucasian 91%	114 (HCC, RCC)	*SLCO1B1*	rs4149056	4.219 [1.05–16.96]						
Leukopenia	Sunitinib	van Erp *et al.* 2009	Caucasian 93.6%	188 (mRCC, GIST)	*CYP1A1* *NR1/3*	rs1048943 rs2307424 rs2307418 rs4073054	6.24 [1.20–32.42] 1.74 [1.02–2.96]	van Erp *et al.* 2009	Caucasian 93.6%	188 (mRCC, GIST)	*FLT3*	rs1933437	0.36 [0.17–0.77]
								Diekstra *et al.* 2015	Caucasian 96%	333 (mRCC)	*VEGFA*	rs3025039	5.42 [1.25–23.5]
								Diekstra *et al.* 2015	Caucasian 96%	372 (mRCC)	*IL-13*	rs1800925	6.76 [1.35–33.9]
								Chu *et al.* 2015	Chinese 89%	97 (RCC)	*FLT3*	rs1933437	8.0 [1.3–51.0]

OR: odds ratio, HR: hazard ratio, mRCC: metastatic renal cell carcinoma, HCC: hepatocellular carcinoma, GIST: gastrointestinal stromal tumor, STS: soft tissue sarcoma, N.A.: not applicable