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ORIGINAL ARTICLE

Sunitinib-induced hypertension in *CYP3A4* rs4646437 A-allele carriers with metastatic renal cell carcinoma

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The single nucleotide polymorphism (SNP) rs4646437G > A in *CYP3A4* was suggested to be related to sunitinib toxicity. Our objective was to perform an in-depth investigation of the association between this SNP and sunitinib toxicity and efficacy using a large cohort of metastatic renal cell carcinoma (mRCC) patients. We collected DNA and clinical information of mRCC patients treated with sunitinib. SNP rs4646437 in *CYP3A4* was tested for associations with toxicity using logistic regression. Cox regression modeling was used for association analysis of rs4646437 with progression-free survival (PFS) and overall survival (OS). In a total of 287 patients, the A-allele of *CYP3A4* rs4646437 was associated with an increased risk for hypertension (odds ratio = 2.4, 95% confidence interval: 1.1–5.2, $P = 0.021$) and showed no significant association with PFS or OS. In conclusion, hypertension is more likely to occur in A-allele carriers of the *CYP3A4* rs4646437 variant in our cohort of mRCC patients treated with sunitinib.

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INTRODUCTION

Sunitinib, a tyrosine kinase inhibitor, is widely prescribed for treatment of metastatic renal cell carcinoma (mRCC).[1] The large inter-individual variability in sunitinib response makes it difficult to predict treatment outcome in individual patients. Sunitinib-induced adverse events lead to dose reductions or treatment discontinuation with subsequent loss of treatment efficacy. This large variability can be explained not only by patient characteristics (for example drug–drug interactions, treatment adherence and environmental factors) but also by the genetic profile of patients. Studies using the candidate gene approach have identified single nucleotide polymorphisms (SNPs) to be associated with the efficacy and risk of toxicity on sunitinib treatment.[1–5]

Sunitinib is metabolized by CYP3A4 to its active metabolite SU12662. Urun *et al.*[6] have observed that A-allele carriers of *CYP3A4* rs4646437G > A showed a lower risk of grades 3–4 toxicity (odds ratio (OR) = 0.27, 95% confidence interval (CI): 0.08–0.88, $P = 0.03$) compared with wild-type (WT) GG in a cohort of 159 European mRCC patients treated with sunitinib. In a small number of reports on other types of drugs that are metabolized by CYP3A4, the variant A-allele of rs4646437 was associated with either an increased or decreased activity of CYP3A4.[7–9] He *et al.*[7] tested 22 SNPs in genes encoding CYP3A4, CYP3A5 and CYP2C19 for associations with voriconazole pharmacokinetics (PK) in a sample of 158 patients. The presence of A-allele of rs4646437 was associated with high plasma voriconazole concentrations of $> 4\ \mathrm{mg\ l^{-1}}$ (OR = 2.8, 95% CI: 1.09–7.38, $P = 0.03$). The authors note that, although rs4646437 is located in the intron (99767460G > A), it could alter the splicing of primary transcripts or gene expression of *CYP3A4*.[7] In another cohort of 240 Chinese renal transplant recipients receiving tacrolimus, Li *et al.*[8] assessed 17 SNPs in *CYP3A5*, *CYP3A4*, *COMT*, *IL-10* and *POR* for association with tacrolimus PK. For rs4646437, a significant association was observed with dose-adjusted tacrolimus blood concentration (C_0/D) showing lower ratios for the variant A-allele carriers.[8] Crettol *et al.*[9] studied 73 patients receiving cyclosporine and reported that A-allele carriers of rs4646437 needed a higher dose of cyclosporine.

A potential explanation for the conflicting results of rs4646437 variant on CYP3A4 expression and metabolism may be related to gender. Schirmer *et al.*[10] reported that rs4646437 is a sex-dependent genetic marker with a higher CYP3A4 expression and activity for female A-allele carriers compared with male A-allele carriers. Therefore, it was suggested to take gender into account in the genetic analyses of *CYP3A4*.[10]

The aim of the current study was to establish whether there is a relationship between rs4646437 in *CYP3A4* and sunitinib treatment outcome in a large cohort of clear cell mRCC patients.

MATERIALS AND METHODS

Study population

This exploratory *post-hoc* analysis is one of the largest pharmacogenetic studies in mRCC patients. In this large observational study, DNA samples together with clinical information were collected from previous pharmacogenetic studies on sunitinib-treated clear cell mRCC patients enrolled between 2004 and 2010 (Figure 1). The SUTOX consortium is a Dutch

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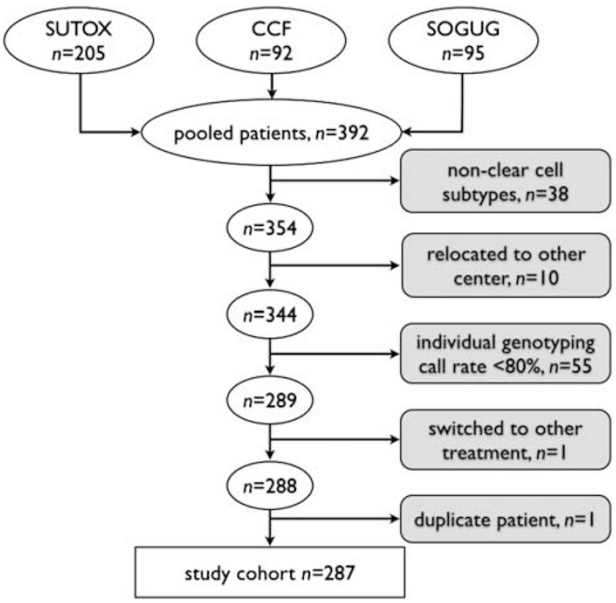

Figure 1. Patient flowchart on included patients. A total of 105 patients had to be excluded from association analyses because of non-clear cell subtypes ($n = 38$), relocation to another medical center during follow-up ($n = 10$), individual genotyping call rates $< 80\%$ ($n = 55$), double patient ($n = 1$) or a change to another treatment than sunitinib directly after enrolment ($n = 1$). A total of 287 sunitinib-treated metastatic renal cell carcinoma patients were available for analysis of toxicity and survival in the present study. CCF, cleveland clinic foundation; SOGUG, Spanish oncology genitourinary group; SUTOX, dutch SUTOX consortium.[11]

working group focusing on genotype-related sunitinib-induced toxicity and comprises five medical centers in the Netherlands. The Spanish Oncology Genitourinary Group (SOGUG) consists of 15 Spanish medical centers, and CCF is the Taussig Cancer Institute of Cleveland Clinic Foundation in the United States.[1–5,11] SUTOX samples were anonymized by a third party, according to the instructions stated in the Codes for Proper Use and Proper Conduct in the Self-Regulatory Codes of Conduct (www.federa.org). The Medical Ethical review boards of all participating centers approved the study. Patients provided their written informed consent for participation.[2,11]

Genotyping methods

Germline DNA was isolated from EDTA-whole blood, peripheral blood mononuclear cell samples, serum or plasma. Samples from serum or plasma were preamplified in order to have a higher DNA concentration. DNA samples from SUTOX and CCF patients were genotyped at Leiden University Medical Center using Taqman probes (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands) on the LightCycler480 (LC480) (Roche Applied Science, Almere, The Netherlands) and on ViiA 7500 (Applied Biosystems) Real-Time PCR Instruments. The latter was used for the analysis of preamplified samples for a better fluorescence chart review. DNA samples from SOGUG were genotyped by the Spanish National Cancer Research Centre using a KASPar SNP genotyping system (Kbiosciences, Hoddesdon, UK) and the sequence Detection System 7900HT (Applied Biosystems, Foster City, CA, USA) for fluorescence detection and allele assignment. In all, 5% of the samples were genotyped in duplicate, and no inconsistencies were observed.[11]

Study design

Sunitinib toxicity was evaluated during four 6-week treatment cycles and scored at baseline, week 4 and week 6 of each cycle according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0 or v4.0.[11] Tested toxicity outcomes were thrombocytopenia, leukopenia, mucosal inflammation, hand–foot syndrome, hypertension and any toxicity $>$ grade 2. Toxicities $\geqslant$ grade 3 were considered clinically relevant. Tested toxicity outcomes were adjusted for toxicity grades observed at baseline.[11] Baseline corrected toxicity scores were calculated by subtracting baseline values from the maximum recorded score in four cycles of treatment. Corrected toxicity scores were divided into grades 0–2 and grades 3–4.[11] Patient characteristics considered relevant for suffering any kind of adverse event were age at the start of sunitinib, gender and study center.

For survival analysis, progression-free survival (PFS) was defined as the time in months between the first day of sunitinib and the date of progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumours version 1.0. If a patient had not progressed, PFS was censored at the time of the last follow-up or date of death. Overall survival (OS) was defined as the time in months between the first day of sunitinib and the date of death or the date at which patients were last known to be alive (last follow-up date). Variables considered to affect PFS or OS were age at the start of sunitinib, gender, study center and prognostic risk group according to Heng criteria.[11–12]

Statistical analysis

Genotyping results were dichotomized in a dominant model with WT (GG genotype) vs A-allele carriers (AG and AA genotype), analogous to the work of Urun *et al*.[6] Distribution of genotypes was tested for deviation from Hardy–Weinberg equilibrium using a χ^2 goodness-of-fit test. Distribution of the continuous variable 'age at the start of sunitinib' followed a normal distribution according to the Shapiro–Wilk test.

SNP rs4646437 (WT vs A-allele carriers) was tested univariately against toxicity end points using a χ^2 test. For multivariate analysis, SNP rs4646437 was tested against toxicity end points dichotomized as grades 0–2 and grades 3–4 using binary logistic regression ($P < 0.05$), including the covariates age at the start of sunitinib, gender and study center.[11]

For PFS and OS analysis, age, gender, study center and Heng prognostic risk group[12] together with *CYP3A4* rs4646437 genotype were included in the multivariate Cox regression survival analysis. All results with a *P*-value < 0.05 from multivariate analyses were considered significant.

In addition, the interaction between the SNP rs4646437 genotypes and gender was tested univariately for association with all of the toxicity outcomes and with PFS and OS.[10–11] This additional analysis was performed to see whether the interaction term of SNP $\times$ gender needed to be included as covariate in multivariate analysis. Interaction between gender and the rs4646437 genotype on PFS and OS was also tested using Cox regression survival analysis.

All tests were two sided and carried out using SPSS Statistical Package for Windows (version 20.0; IBM, Armonk, NY, USA).

RESULTS

Of the initial 391 patients, 287 clear cell mRCC patients met the inclusion criteria of which 68% were males (Figure 1). Baseline patient characteristics are summarized in Table 1. Genotype frequencies were 228 carriers of WT GG, 52 carriers of heterozygous AG and 7 carriers of the AA genotype. This is consistent with Hardy–Weinberg equilibrium ($\chi^2 = 3.46$, $P = 0.063$). Obtained minor allele frequency was 6.97%.

Most patients had no toxicities at baseline (95.5–100% for the tested toxicities). Baseline grades 1–3 toxicities were observed for 0–4.5% of patients, and no baseline grade 4 toxicities were observed. Dose reductions were needed for 33% of patients within cycles 1–4 of sunitinib. Any toxicity $>$ grade 2 was observed in 25% of patients (Table 2). Observed grades 3–4 adverse events within four cycles of sunitinib were thrombocytopenia (7.7%) leukopenia (2.8%), mucosal inflammation (3.1%), hand–foot syndrome (5.2%) and hypertension (13.6%). The interaction between SNP genotype and gender was tested against all toxicity outcomes, but no significant interaction was found in univariate analysis ($P = 0.27$). As a result, gender was included as an independent covariate instead of a combined 'gender $\times$ SNP' covariate. Genotype distributions for males and females are presented in Table 1. Table 3 shows the results of association analyses. For A-allele carriers of *CYP3A4* rs4646437, we observed an increased risk for hypertension (OR = 2.4, 95% CI: 1.1–5.2, $P = 0.021$). For other toxicity end points, no significant associations were observed.

Table 1. Baseline characteristics of clear cell metastatic renal cell carcinoma patients treated with sunitinib ($n = 287$)

Feature	*Value (range)*	*%*
Gender		
Male	195	68
Female	92	32
Median age at the start of sunitinib, years	61 (34–87)	
Mean BSA	1.97 (1.2–2.7)	
Prior nephrectomy		
Yes	242	84.3
No	41	14.3
Unknown	4	1.4
WHO performance status		
0	120	42
1	142	50
2	17	6
3	1	0
Unknown	7	2
Ethnicity		
Caucasian	277	97
Black	4	1
Asian	2	1
Arab	3	1
Latin American	1	0
Gender genotype distributions		
Female AA carriers	2	1
Female AG carriers	17	6
Female GG carriers	73	25
Male AA carriers	5	2
Male AG carriers	35	12
Male GG carriers	155	54
Heng prognostic risk group[a]		
Good (0 risk factors)	61	21
Intermediate (1–2 risk factors)	157	55
Poor (3–6 risk factors)	69	24
Prior systemic antitumor treatment		
Yes	52	18
No	235	82
Sunitinib daily dose (mg)		
Only 50	269	94
Only 37.5	14	5
Only 25	4	1
Dose reduction after cycle 1, 2 or 3		
No	180	63
Yes	95	33
Unknown	12	4
Best response to sunitinib		
Complete response	9	3
Partial response	120	42
Stable disease	104	36
Progressive disease	37	13
Unknown	17	6
Median SBP (mm Hg)	140 (95–205)	
Median DBP (mm Hg)	80 (29–110)	
Median LDH (U l^{-1})	241 (110–1190)	
Median creatinine (μmol l^{-1})	106.1 (1.0–247.5)	
Median bilirubin (μmol l^{-1})	6.84 (0.5–46.2)	
Median albumin (g l^{-1})	42 (4.7–51.0)	
Median AST (U l^{-1})	19 (8–107)	
Median ALT (U l^{-1})	17 (4–119)	
Median hemoglobin (mmol l^{-1})	8.1(4.7–14.2)	

The median PFS was 17 months with a median follow-up period of 45 months for PFS analysis. The median follow-up period was 49 months for OS and the median OS was 29 months. The interaction between gender and genotype was tested in PFS and OS analysis, but no significant interaction was found ($P = 0.23$ and $P = 0.76$ respectively). There was no significant difference in median PFS or median OS between *CYP3A4* rs4646437 WT and A-allele carrier patients both uncorrected and corrected for age, gender, study center and Heng prognostic risk group in Cox regression survival analysis (Table 3).

DISCUSSION

In this study, we observed a significant association between the presence of A-allele in *CYP3A4* rs4646437 and an increased risk for hypertension compared with WT carriers in sunitinib-treated mRCC patients. Hence, *CYP3A4* rs4646437 is a potential predictive biomarker for hypertension in sunitinib-treated mRCC patients, but this needs confirmation.

This is the first time that SNP *CYP3A4* rs4646437 is examined in a large cohort of mRCC patients. Grades 3–4 hypertension was observed in 14% of patients both in this study and in the study of Urun *et al*.[6] Our findings do not confirm the data of Urun *et al*.,[6] who observed no association with hypertension and who reported a reduced risk of grades 3–4 toxicities for AG carriers of *CYP3A4* rs4646437 (OR = 0.27). In contrast to earlier reports, we did not demonstrate significant results for the interaction between genotype and gender.[10]

Our studied time period of four treatment cycles in which toxicity data were collected is comparable to Urun *et al*.[6] who reported a median treatment duration of 7.7 months. In both studies, Caucasians were included of whom the majority were male.[6] The difference in our findings with those of the group of Urun *et al*.[6] could partly be explained by our large sample size (287 vs 159 patients), a higher number of A carriers (20.6% vs 11.2%) and a lower rate of adverse events >grade 2 (24.7% vs 52%). In addition, our fixed covariates in multivariate testing ($P < 0.1$) differ from the included clinical covariates by Urun *et al*.[6] using a significance threshold of $P < 0.2$. The time frame of our study is long including 7 years, which could introduce a bias as clinical experience with sunitinib may have caused dose reduction before the occurrence of >grade 2 adverse events. A time-to-event analysis is preferred for toxicity analysis as many patients will not complete four cycles of sunitinib treatment, and patients may develop toxicities earlier or later in this time frame. However, it was not possible to collect these data accurately because of the retrospective character of this study.

Table 1. (Continued)

Feature	*Value (range)*	*%*
Median leukocytes ($\times 10^9$)	7.6 (1.6–50.0)	
Median neutrophils ($\times 10^9$)	4.8 (0.7–26.4)	
Median thrombocytes ($\times 10^9$)	254 (92–1492)	
Median MCV (fl)	88 (68–110)	
Median calcium (mmol l^{-1})	2.38 (1.92–2.93)	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BSA, body surface area; DBP, diastolic blood pressure; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; SBP, systolic blood pressure; WHO, world health organization (performance status). [a]Patients are grouped according to their Heng risk group based on the six Heng risk scores: detoriated WHO performance status (⩾2), low hemoglobin (< lower limit of normal), high calcium (>2.5 mmol l^{-1}), time from initial diagnosis to treatment with sunitinib (< 1 year), neutrophil count (greater than upper limit of normal) and thrombocytes (greater than upper limit of normal).[11]

Table 2. Distribution of baseline corrected toxicity scores within four cycles of sunitinib treatment

Type of toxicity	*Toxicity grade*	*Number of patients (n)*	*Percentage of patients (%)*
Thrombocytopenia	None	104	36
	Grade 1	122	43
	Grade 2	39	14
	Grade 3	18	6
	Grade 4	4	1
Leukopenia	None	151	53
	Grade 1	78	27
	Grade 2	50	17
	Grade 3	8	3
Mucosal inflammation	None	126	44
	Grade 1	93	32
	Grade 2	59	21
	Grade 3	9	3
Hand–foot syndrome[a]	None	173	60
	Grade 1	57	20
	Grade 2	42	15
	Grade 3	15	5
Any toxicity >grade 2	None	39	14
	Grade 1	76	26
	Grade 2	101	35
	Grade 3	62	22
	Grade 4	9	3
Hypertension	None	173	60
	Grade 1	29	10
	Grade 2	45	16
	Grade 3	39	14

In case the grade of toxicity was not recorded in the medical record of the patient, it was assumed that no toxicity had occurred (grade 0). [a]For hand–foot syndrome, grade 3 is the highest possible grade according to CTCAE version 4.0.

Table 3. Association analysis results of *CYP3A4* rs4646437 vs toxicity end points and survival end points

Toxicity end point	P-value	*OR*	*95% CI*	
			Lower	*Upper*
Thrombocytopenia grades 0–2 vs 3–4				
WT vs A carriers uncorrected	0.18	0.31	0.08	1.61
WT vs A carriers	0.21	0.38	0.08	1.74
Leukopenia grades 0–2 vs 3–4				
WT vs A carriers uncorrected	0.57	0.54	0.07	4.5
WT vs A carriers	0.78	0.73	0.08	6.4
Mucositis grades 0–2 vs 3–4				
WT vs A carriers uncorrected	0.90	1.11	0.22	5.48
WT vs A carriers	0.72	1.37	0.25	7.5
Hand–foot syndrome grades 0–2 vs 3–4[a]				
WT vs A carriers uncorrected	0.07	2.76	0.94	8.08
WT vs A carriers	0.14	2.33	0.77	7.09
Hypertension grades 0–2 vs 3–4				
WT vs A carriers uncorrected	0.013	2.51	1.21	5.22
Wt vs A carriers	**0.021**	2.43	1.14	5.18
Any toxicity >grade 2				
WT vs A carriers uncorrected	0.59	0.83	0.42	1.64
WT vs A carriers	0.89	0.95	0.46	1.96
Survival end point	P-*value*	*HR*	*95% CI*	
			Lower	*Upper*
PFS				
WT vs A carriers uncorrected	0.38	0.86	0.61	1.20
WT vs A carriers	0.14	0.77	0.55	1.09
OS				
WT vs A carriers uncorrected	0.92	1.02	0.71	1.47
WT vs A carriers	0.45	0.86	0.59	1.26

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival; WT, wild type. In case the grade of toxicity was not recorded in the medical record of the patient, it was assumed that no toxicity had occurred (grade 0). Toxicity end points are corrected for age, gender and study center. Survival end points are corrected for age, gender, Heng prognostic risk group and study center. [a]For hand–foot syndrome, grade 3 is the highest possible grade according to CTCAE version 4.0. Values in bold represent *P*-values < 0.05 corrected for clinical covariates.

The expression of CYP3A4 in the liver is twofold higher in women than in men that can be explained by sex-dependent gene expression differences.[10] However, as genders are not equally present in this study (only one-third is female) and merely 19 subjects (7%) were female A carriers, it is not possible to perform robust statistics for interaction testing between gender and SNP genotype.

Based on our results in this large cohort, it remains difficult to explain whether A-allele carriers of *CYP3A4* rs4646437 either have an increased or decreased function of CYP3A4. One could reason that an increased function would lead to conversion of sunitinib to the metabolite SU12662 with a similar activity and a longer half-life compared with the parent compound. On the other hand, a decreased function of CYP3A4 could lead to an increase in total drug exposure all the same. In both hypotheses, A-allele carriers will have an increased exposure to the drug with a stronger inhibition of vascular endothelial growth factor receptor 2 (VEGFR-2) and therefore a higher risk of hypertension.[2–4,13]

A number of PK/pharmacodynamic analyses demonstrate that the increased plasma drug exposure of sunitinib (and SU12662) indeed results in hypertension or other types of toxicity. In a large meta-analysis of Houk *et al*.[14] on mainly Caucasian patients, it was shown that a higher exposure to sunitinib and SU12662 (total drug AUC) resulted in improved clinical outcomes and an increased risk of adverse events: fatigue, diastolic blood pressure elevation, or reduction of the absolute neutrophil count. Also, in a PK analysis of Mizuno *et al*.[15] on 19 Japanese RCC patients, the systemic exposure to sunitinib and its active metabolite was associated with the incidence of thrombocytopenia ($\geqslant$ grade 2) and hypertension ($\geqslant$ grade 2). Nagata *et al*.[16] studied six Japanese RCC patients of whom four received a starting dose of 50 mg and developed grade 2 or 3 thrombocytopenia. It was concluded that the total trough level of sunitinib should be < 100 ng ml^{-1} in order to avoid severe thrombocytopenia and the starting dose could be reduced to 37.5 or 25 mg in most cases. In another PK analysis, Noda *et al*.[17] investigated 21 RCC patients on the association of total sunitinib concentration with toxicities and clinical outcome. Patients with a total sunitinib concentration $\geqslant 100$ ng ml^{-1} showed a higher incidence of $\geqslant$ grade 3 thrombocytopenia, anorexia or fatigue.[17] Recently, Teo *et al*.[18] investigated the effect of SNPs in *CYP3A5* and *ABCB1* on both PK and clinical outcome (that is, toxicity and response) in a Chinese population of 31 patients. The variant CC genotype of rs1045642 in *ABCB1* was associated with a higher exposure to sunitinib, an increased risk for rash and mucositis and progression of the disease as compared with T-allele carriers ($P < 0.05$). No association with sunitinib exposure, response or toxicities was seen for rs776746 in *CYP3A5*.[18] In contrast, our research group investigated

a considerably larger group of Caucasian patients and reported that rs776746 in *CYP3A5* was associated with hypertension (OR = 4.70, 95% CI: 1.47–15.0, $P = 0.009$) and with the need for dose reductions.[11] Another SNP in *CYP3A4* (*CYP3A4*22*) was tested in a set of 114 patients and associated with a 22.5% decrease in clearance of sunitinib, which explains the higher exposure to the drug.[19] However, this pharmacogenetic–PK analysis did not investigate the occurrence of toxicities and the SNP is different from that in the present study. In putting together these results, we should be aware that patients of Asian ethnicity have been reported to have a higher incidence of severe sunitinib-induced toxicities compared with Caucasians.[11,14–18]

Remarkable in our findings is that only an association was observed of SNP rs4646437 with sunitinib-induced hypertension, whereas no associations have been found with any of the other tested toxicities on sunitinib. Although mechanisms are currently not fully unraveled, it is thought that sunitinib-induced hypertension is caused by inhibition of VEGFR-2 leading to a reduced amount of nitric oxide and thus vasoconstriction. SNPs in *VEGFA* and *eNOS* are reported to be related to sunitinib-induced hypertension.[4,11,13] Probably there are more factors involved that influence the development of hypertension, which can be related to both PK and pharmacodynamics. The current study and other recent findings of our group suggest that SNPs in *CYP3A4* and *CYP3A5* could have an essential role in hypertension development.[11]

Furthermore, hypertension can be considered as a different sort of toxicity as it is related to improved clinical outcomes on sunitinib.[4,20] Yet, no improved survival outcomes were seen for the variant A-allele carriers of rs4646437. Promising biomarkers for sunitinib efficacy have been identified in *ABCB1*. Corresponding results were observed for SNPs in *ABCB1*: the presence of WT CGT haplotype in rs1128503, rs2032582 and rs1045642 resulted in an improved clinical outcome (PFS, OS and response), the CC WT in rs1128503 showed a decrease in sunitinib clearance, and the TT variant in rs1128503 required less dose reductions.[11,19,21] In contrast, the variant CC genotype of rs1045642 showed an increased exposure to sunitinib in Japanese patients.[18] To predict hypertension and subsequent effects on survival, we may be searching for one biomarker that consists of multiple SNPs related to the PK and pharmacodynamics of sunitinib.

In conclusion, hypertension is more likely to occur in A-allele carriers of the *CYP3A4* rs4646437 variant. Confirmation of this finding in another cohort is needed to potentially use this SNP as a predictive biomarker for hypertension on sunitinib treatment.

CONFLICT OF INTEREST

Brian Rini and Garcia-Donas report consulting and research funding from Pfizer. The other authors declare no conflict of interest.

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