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Pharmacogenomic Markers of Targeted Therapy Toxicity in Patients with Metastatic Renal Cell Carcinoma

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Abstract

Background—Targeted therapy (TT) in metastatic renal cell carcinoma (mRCC) may be associated with a high rate of toxicity that undermines treatment efficacy and patient quality of

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We observed an association between a *CYP3A4* polymorphism and toxicity outcomes in patients with metastatic renal cell carcinoma treated with sunitinib, but not with everolimus or temsirolimus. We did not observe other associations previously reported.

Author contributions: Toni K. Choueiri had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Choueiri, Pomerantz, Freedman, Urun, Signoretti, McDermott.
Acquisition of data: Carol, Fay, Signoretti, Urun, de Velasco.
Analysis and interpretation of data: de Velasco, Gray, Hamieh, Urun, Signoretti, Choueiri.
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life. Polymorphisms in genes involved in the pharmacokinetic pathways of TTs may predict toxicity.

Objective—To investigate whether selected single-nucleotide polymorphisms (SNPs) in three core genes involved in the metabolism and transport of sunitinib and the mTOR inhibitors everolimus and temsirolimus are associated with adverse events (AEs).

Design, setting, and participants—Germline DNA was extracted from blood or normal kidney tissue from mRCC patients of Caucasian ethnicity in two cohorts treated with either sunitinib (n = 159) or mTOR inhibitors (n = 62). Six SNPs in three candidate genes (*CYP3A4*: rs2242480, rs4646437, and rs2246709; *CYP3A5*: rs15524; and *ABCB1*: rs2032582 and rs1045642) were analyzed.

Outcome measurements and statistical analysis—Primary endpoints were grade ≥3 AEs for all patients; grade ≥3 hypertension in the sunitinib cohort, and any grade pneumonitis in the mTOR inhibitors cohort. A logistic regression model was used to assess the association between SNPs and AEs, with adjustment for relevant clinical factors.

Results and limitations—In total, 221 samples were successfully genotyped for the selected SNPs. In the sunitinib cohort, the *CYP3A4* rs464637 AG variant was associated with a lower risk of high-grade AEs (odds ratio 0.27, 95% confidence interval 0.08–0.88; p = 0.03), but no SNPs were associated with hypertension. In the mTOR inhibitor cohort, none of the selected SNPs was associated with any toxicity.

Conclusions—We observed an association between *CYP3A4* polymorphisms and toxicity outcomes in mRCC patients treated with sunitinib, but not with everolimus or temsirolimus. Our findings are exploratory in nature, and further validation in independent and larger cohorts is needed.

Patient summary—We found that variants of *CYP3A4*, a gene involved in drug metabolism, are associated with sunitinib toxicity. This information may help in better selection of patients for targeted therapies in metastatic renal cell carcinoma.

Keywords

Biomarker; Genomics; Polymorphisms; Renal cell carcinoma; Single-nucleotide polymorphism; Targeted therapy

1. Introduction

The introduction of targeted therapy (TT) in the management of metastatic renal cell carcinoma (mRCC) has led to improved outcomes at the expense of side effects associated with treatment [1]. Since mRCC remains an incurable disease, quality of life (QoL) is an important consideration for patients. During the last decade, two different types of TT agents have been used for the treatment of mRCC: vascular endothelial growth factor-TT (VEGF-TT), mainly TKIs (tyrosine kinase inhibitors); and mTOR inhibitors. These drugs are generally well tolerated, but major toxicities frequently arise. Some series show that up to 50% of patients can develop grade ≥3 toxicities, and a significant number experience adverse events (AEs) leading to treatment interruption, dose reduction, and drug

discontinuation [2]. Therefore, individual variability in drug efficacy resulting in therapeutic failure is an important issue. Identification of genomic variants may aid in the development of strategies for patient selection that could lead to improved adherence to treatment and better QoL. Moreover, pharmacogenomics may reduce costs and improve optimal drug development [3].

The mechanism underlying TT toxicity is complex and not entirely understood [4]. While fatigue/asthenia, rash, and diarrhea are common to both sunitinib and mTOR inhibitors, other AEs are class-specific [1,2]. For example, sunitinib is associated with higher incidence of hypertension and hand-foot syndrome, while higher incidence of infections, pneumonitis, hypercholesterolemia, and hyperglycemia has been observed for mTOR inhibitors [2].

Clinical determinants of TT toxicity, such as age, female gender, and low body-surface area, only partly explain the interindividual variability in drug toxicity [5]. Patients with similar clinical characteristics may exhibit wide variability in tolerability for the same drug according to their genetic background [6]. Single-nucleotide polymorphisms (SNPs) in the pharmacokinetic (PK) and pharmacodynamic (PD) pathways for TT agents have been postulated as a complementary explanation for this heterogeneous toxicity [3]. Not all TTs in the same class have the same toxicity profiles, and SNPs may contribute to shape these differences [7]. Sunitinib and mTOR inhibitors are significantly metabolized by cytochrome P450 proteins, predominantly CYP3A4, leading to variation in serum concentrations of the drugs [8,9]. Similarly, concentrations may differ according to polymorphisms in transporters such as ABCB1 [10]. Therefore, SNPs of genes involved in drug PK pathways affect the frequency and severity of drug toxicities in mRCC [11,12]. However, no individual SNP is currently used as a risk factor for TT toxicity in mRCC.

The aim of our study was to assess the association between six SNPs in three core genes implicated in the metabolic and transport pathways for sunitinib and mTOR inhibitors and the risk of grade ≥3 AEs and class-specific AEs such as hypertension in the sunitinib cohort and pneumonitis in the mTOR inhibitor cohort.

2. Patients and methods

2.1. Patients

The cohort comprised 221 mRCC patients who received at least one cycle (4 wk on treatment) of sunitinib or mTOR inhibitors as TT at the Dana-Farber/Harvard Cancer Center (DF/HCC) between January 2005 and December 2011 and for whom genotyping was successful. Patients were exclusively of Caucasian ethnicity to ensure no admixture due to ancestry [13]. All patients provided written informed consent. The institutional review board for DF/HCC approved the study. Clinical data were ascertained from medical records in a prospective database. High-grade and class-specific AEs (high-grade hypertension for sunitinib and all-grade pneumonitis for the mTOR inhibitors) were recorded during the treatment period and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

2.2. Blood sample collection, DNA extraction, and genotyping

Germline DNA was extracted from peripheral whole blood using a QIAamp DNA Blood mini kit (Qiagen, Valencia, CA, USA) or from formalin-fixed, paraffin-embedded blocks of normal kidney parenchyma (by an expert genitourinary pathologist) using a DNeasy 96 Blood & Tissue kit (Qiagen). Isolated DNA was genotyped for six polymorphisms in three candidate genes (Supplementary Table 1): *CYP3A4* (rs2242480, rs4646437, rs2246709), *CYP3A5* (rs15524), and *ABCB1* (rs2032582, rs1045642). The SNPs were selected from the European-American ancestry population of the HapMap database according to the following criteria: (1) involvement in the PK pathways for sunitinib and mTOR inhibitors; (2) assumed clinical relevance on the basis of previous reports [12]; (3) a minimal allele frequency of 5%; and (4) tagged across the gene (including both exons and introns) with a minimum correlation index (r2) of 80%.

Genotyping was performed using the iPlex Gold platform (Sequenom, San Diego, CA, USA) with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. All SNP assays were combined into a 12-multiplex pool design, and all reactions were carried out in 384-well format. For quality control purposes, 5% of the duplicate samples were randomly selected and interspersed among plates. The concordance rate for duplicate genotyping was 100%. Analysis was restricted to SNPs passing quality filters; SNPs with a genotyping success rate <85% or with significant deviation from Hardy-Weinberg equilibrium (HWE) were excluded.

2.3. Statistical analysis

Patient characteristics were summarized as median with interquartile range (IQR) for continuous variables and as number and percentage for categorical variables. The primary analysis endpoints were grade ≥3 AEs (all patients), grade ≥3 hypertension (sunitinib cohort) and any-grade pneumonitis (mTOR inhibitors cohort). A logistic regression model was used to test the association between the genotype variants and the targeted AEs in univariate and multivariable analyses adjusted for relevant clinical factors based on p-value 0.25 (for the coefficient estimate) to indicate potential associations of the covariate with targeted AEs), using genotype model that compared variant (rare) homozygote or heterozygote versus wild-type homozygote (reference).

All genotypes were tested for HWE deviation. No significant violations were observed for the cohorts (Supplementary Table 1).

Results are presented in accordance with REMARK criteria [14]. All statistical tests were two-sided. Given that this is a targeted analysis with a specific hypothesis to assess the associations between preselected gene polymorphisms and specific AE types, no multiple-comparison adjustments were applied, and $p < 0.05$ was considered statistically significant.

3. Results

DNA was extracted and successfully genotyped for 221 patients with mRCC who received either sunitinib ($n = 159$) or temsirolimus or everolimus as an mTOR inhibitor ($n = 62$). All patients were Caucasian, and 81% had clear-cell RCC (Table 1).

3.1. Sunitinib cohort

In the sunitinib cohort, the median age was 61 yr (IQR 53-67); 72% of the patients were male and 90% had clear-cell RCC histology. The median treatment duration was 7.6 mo (IQR 3.0–15.9). Overall, 83 (52%) patients reported grade ≥3 AEs and 22 (14%) reported high-grade hypertension. No associations between AEs and gender, age at the start of therapy, treatment duration, and Memorial Sloan Kettering Cancer Center criteria/risk group were observed (Supplementary Table S2). The *CYP3A4* rs464637 AG variant was associated with a lower risk of grade ≥3 AEs (odds ratio [OR] 0.27, 95% confidence interval [CI] 0.08–0.88; $p = 0.03$) when compared to the GG wild type (Table 2). No associations between other SNPs and grade ≥3 AEs or hypertension were observed (Table 2).

3.2. mTOR inhibitor cohort

Among the 62 patients included in the analysis, the median age was 60 yr (IQR 55-67), and 74% had clear-cell RCC histology, with 65% ($n = 40$) receiving temsirolimus and 35% ($n = 22$) everolimus. The median treatment duration was 3.3 mo (IQR 1.5–6.1). Twenty-one (34%) patients reported grade ≥3 AEs and 26 (42%) experienced any grade of pneumonitis. There was no association observed between the selected SNPs and all high-grade AEs or any grade-pneumonitis for any of the genotypes (Table 3).

4. Discussion

We hypothesized that variability in drug toxicity has a heritable component. We interrogated inherited variants for key genes involved in drug metabolism to develop a genetic risk profile. An accurate profile could facilitate individualization of treatment and minimization of toxicity [15]. In our series, in line with published data, most mRCC patients receiving TT experienced side effects, and up to 50% developed grade ≥3 toxicity [16]. Since TT is a noncurative therapy for mRCC and QoL is an important consideration, there is great interest in identifying patients at high risk of toxicity [15]. Efforts have been made to tailor individual therapy and predict toxicity, including PK/PD monitoring and toxicity-based titration [17,18]. It has been shown that variations in genes related to sunitinib-metabolizing enzymes influence individual responses and tolerability [11,12,19]. However, no upfront biomarkers are currently available to predict toxicity in mRCC patients. The development of genomic toxicity biomarkers in cancer treatment is a complex process, but successes have been reported. Several pharmacogenetic tests to minimize toxicity are already approved by the US Food and Drug Administration [20]. For example, testing for the *DPYD* gene in patients receiving 5-fluorouracil may help to avoid up to 30% of life-threatening toxicities [21]. Clinical risk models have also been developed to predict toxicity-related treatment discontinuation in mRCC patients receiving VEGF-TT [22]. Although not currently implemented in clinical practice, these models may complement germline genetic variant testing.

In our study we analyzed the association between genotype and drug toxicity (sunitinib/mTOR inhibitors), focusing on inherited variants in key shared genes in the PK pathway, namely *CYP3A4*, *CYP3A5*, and *ABCB1*. We found a positive association between the A allele at *CYP3A4* rs464637 and lower high-grade toxicities in the sunitinib cohort.

Conversely, Diekstra et al [23] observed an association between the *CYP3A4* rs4646437 A allele and higher risk of hypertension among 285 mRCC patients treated with sunitinib, but no association with high-grade toxicities. There are some relevant variations that may explain this discrepancy in results. First, the same group failed to replicate 20 out of 22 SNPs from previous well-designed studies, which reflects the complexity of this type of study [11]. Second, compared to a previous study in which the same cohort ($n = 333$) was analyzed, in the latest study by the Diekstra group the genotyping call rate was <80% for 55 individuals [23], much higher than in previous studies reported. Although our approach was more restrictive, excluding SNPs with a genotyping success rate <85%, we only excluded eight patients for that specific SNP. Finally, the study cohorts may not be comparable: ours was a single-institution study including only Caucasian patients, whereas Diekstra et al included 3% non-Caucasian patients in a multicenter study. Furthermore, clinical variables such as prior nephrectomy and prior line of therapy differ substantially between the studies, which may also affect the results.

CYP3A4 plays a major role in metabolism, affecting more than half the drugs in clinical use [24]. It has been shown that genetic and nongenetic factors affect CYP3A4 expression, with wide interindividual variability of up to 50-fold. These differences affect the clearance of several drugs [24]. CYP3A4 metabolizes sunitinib to its active metabolite SU12662, for which higher levels have been associated with better outcome [25]. Although some *CYP3A4* SNPs have been associated with protein expression and enzyme activity in human liver microsomes, rs4646437 does not affect allelic mRNA expression, mRNA levels, or enzyme activity [26]. In light of these particular circumstances, the association might imply subtle differences in expression or other factors not well understood.

In contrast to other studies, we focused only on genes related to sunitinib metabolism rather than less specific genes such as *KDR* and *VEGFA*, and we also included for the first time a group of patients treated with standard mTOR inhibitors [11].

Table 4 lists data previously reported for *CYP3A4*, *CYP3A5*, and *ABCB1* SNPs and their associations with toxicity outcomes. It has been shown that some SNP associations previously reported are false-positives, and these have been retracted from the literature [27]. Admixture based on ancestry is another concern that we addressed by including patients of only European ancestry [13], although this affects the generalizability of our data to other ancestral populations. Ethnic differences in polymorphisms have been clearly reflected in differences in toxicity profiles, such as the higher rate of sunitinib-induced AEs among Asian patients [28].

Evaluation of a large number of candidate SNPs and endpoints carries a high risk of false-positive associations, especially when findings have not been adjusted for multiple testing. This is the reason why we chose a low number of exploratory SNPs and focused on the three most important genes in the metabolism and clearance of sunitinib and mTOR inhibitors. In addition, the number of patients in our cohort is either similar to or greater than in previous studies [19,29].

Our work represents a basis for further exploration of associations between genotype and toxicity, bearing in mind it is the first study reporting associations that includes both sunitinib and mTOR inhibitor cohorts. Although our study may be underpowered for detect of associations with specific AEs such as hypertension and pneumonitis, we were able to identify associations with grade 3 sunitinib-related side effects. Replication and validation of studies such as this are challenging, but may be possible by accessing large cooperative studies such as IMDC and EuroTARGET. In addition, adjuvant trials in RCC such as ECOG 2085 have failed to show benefit of TT and it is possible that patient selection based on pharmacogenomic markers could facilitate success in this setting. The new drugs available for mRCC—cabozantinib and nivolumab—have revolutionized the therapeutic landscape for this condition. While our specific study may not be directly translatable to these novel drugs, it provides further insights for the genotyping strategies that are undoubtedly need to meet the challenging therapeutic goals in mRCC.

5. Conclusions

We found a statistically significant association between *CYP3A4* rs4646437 polymorphism and high-grade toxicity in patients treated with sunitinib, whereby patients with the AG variant experienced a lower number of high-grade AEs. Testing for associations between genetic polymorphisms and toxicity is feasible and could potentially guide clinicians in selecting optimal personalized therapies for their patients, rather than using a “one size fits all” approach. This is particularly important in mRCC, for which the treatments approved are sometimes comparable in terms of efficacy but may have different AE profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient characteristics by analysis cohort[a]

Characteristic	Cohort	
	Sunitinib	mTOR inhibitor
Patients (*n*)	159	62
Age (yr)	60.8 (52.8–67.1)	60.3 (54.9–66.6)
Caucasian race[b]	159 (100)	62 (100)
Gender		
Male	114 (72)	46 (74)
Female	45 (28)	16 (26)
ECOG performance status		
0	71 (50)	29 (51)
1	58 (41)	23 (40)
≥2	14 (9)	5 (9)
Unknown	16	5
Histology		
Clear cell	134 (90)	45 (74)
Non–clear cell	15 (9)	16 (26)
Mixed	2 (1)	0
Unknown	10	0
Previous nephrectomy		
Yes	146 (92)	0
No	13 (8)	0
Metastatic sites		
1	41 (26)	15 (25)
2	49 (31)	18 (30)
3	42 (26)	20 (33)
4	20 (13)	6 (10)
≥5	7 (4)	2 (3)
Unknown	0	1
Prior therapy		
Yes	53 (34)	54 (87)
No	103 (66)	8 (13)
Unknown	3	0
Targeted therapy		
Sunitinib	159 (100)	
TMS + bevacizumab		6 (10)
EVS		22 (35)
TMS		31 (50)
TMS/EVS EVS		3 (5)
Treatment duration (mo)	7.6 (3.0–15.5)	3.3 (1.5–6.1)

Characteristic	Cohort	
	Sunitinib	mTOR inhibitor
Analysis endpoint		
Grade ≥3 adverse events	83 (52)	21 (34)
Grade ≥3 hypertension	22 (14)	–
Any-grade pneumonitis	–	22 (35)

ECOG = Eastern Cooperative Oncology Group; TMS = temsirolimus; EVS = everolimus.

[a] Data are reported as median (interquartile range) for continuous variables and as n (%) for categorical variables.

[b] All patients were Caucasian to ensure no admixture due to ancestry.

Table 2

Associations between genotype variants and adverse events in the sunitinib cohort according to multivariable regression[a]

Gene	SNP	Grade ≥3 adverse events			Grade ≥3 hypertension		
		Patients (events)	OR (95% CI)	*p* value	Patients (events)	OR (95% CI)	*p* value
CYP3A4	rs2242480						
	CC	135 (74)	1 (reference)		135 (20)	1	
	TC	19 (6)	0.41 (0.14–1.15)	0.09	19 (1)	0.35 (0.04–2.80)	0.32
CYP3A4	rs4646437[b]						
	GG	134 (73)	1 (reference)		134 (20)	1	
	AG	17 (4)	0.27 (0.08–0.88)	0.03	17 (1)	0.39 (0.05–3.11)	0.37
CYP3A4	rs2246709						
	AA	80 (43)	1 (reference)		80 (10)	1	
	AG, GG	76 (38)	0.88 (0.46–1.68)	0.69	76 (10)	0.82 (0.30–2.24)	0.70
CYP3A5	rs15524[b]						
	AA	142 (77)	1 (reference)		142 (20)	1	
	GA	16 (5)	0.35 (0.11–1.08)	0.07	16 (1)	0.41 (0.05–3.32)	0.41
ABCB1	rs2032582						
	GG	50 (25)	1 (reference)		50 (8)	1	
	GT	71 (38)	1.12 (0.53–2.37)	0.77	71 (10)	0.86 (0.29–2.54)	0.79
	TT	32 (17)	1.15 (0.45–2.91)	0.77	32 (3)	0.57 (0.13–2.46)	0.46
	rs1045642						
	AA	53 (25)	1 (reference)		53 (7)	1	
	GA	68 (36)	1.18 (0.56–2.45)	0.67	68 (9)	0.93 (0.31–2.75)	0.89
	GG	28 (18)	1.96 (0.73–5.25)	0.18	28 (6)	1.44 (0.40–5.19)	0.58

OR = odds ratio; CI = confidence interval

[a]Adjusted for relevant clinical factors of gender, treatment duration, and Memorial Sloan Kettering Cancer Center categories for any associations with adverse events.

[b]No data available for variant/homozygous allele group.

Table 3

Associations between genotype variants and adverse events in the mTOR inhibitor cohort according to multivariable regression[a]

Gene	SNP	Grade ≥3 adverse events			All-grade pneumonitis		
		Patients (events)	OR (95% CI)	*p* value	Patients (events)	OR (95% CI)	*p* value
CYP3A5	rs15524[b]						
	AA	57 (18)	1 (reference)		57 (24)	1 (reference)	
	GA	4 (2)	1.82 (0.18–18.18)	0.61	4 (2)	0.79 (0.09–6.95)	0.83
CYP3A4	rs2242480[b]						
	CC	53 (16)	1 (reference)		53 (22)	1 (reference)	
	TC	6 (4)	3.90 (0.45–33.66)	0.22	6 (4)	5.24 (0.48–57.73)	0.18
CYP3A4	rs4646437						
	GG	54 (17)	1 (reference)		54 (23)	1 (reference)	
	AG	4 (1)	0.43 (0.03–5.47)	0.51	4 (2)	1.20 (0.14–10.36)	0.87
	rs2246709						
	AA	29 (11)	1 (reference)		29 (14)	1 (reference)	
	AG, GG	32 (9)	0.72 (0.19–2.73)	0.63	32 (12)	0.35 (0.09–1.28)	0.11
ABCB1	rs2032582						
	GG	22 (7)	1 (reference)		22 (9)	1 (reference)	
	GT	25 (10)	3.51 (0.69–17.92)	0.13	25 (12)	2.61 (0.63–10.83)	0.19
	TT	13 (4)	1.15 (0.19–7.11)	0.88	13 (5)	1.14 (0.21–6.33)	0.88
	rs1045642						
	AA	25 (12)	1 (reference)		25 (10)	1 (reference)	
	GA	27 (7)	0.41 (0.08–2.12)	0.29	27 (12)	0.87 (0.22–3.40)	0.84
	GG	7 (1)	0.38 (0.03–4.51)	0.45	7 (2)	0.60 (0.07–4.90)	0.65

[a] Adjusted for potentially significant clinical factors of age, therapy duration, and Memorial Sloan Kettering Cancer Center categories for any association with adverse events.

[b] No data available for variant/homozygous allele group.

Table 4

***CYP3A4*, *CYP3A5*, and *ABCB1* SNP associations with toxicity outcomes reported in previous studies**

Study	Patient cohort (*n*)	Toxicity outcome	SNP	OR (95% CI)	*p* value	Multiple testing
Diekstra [23]	mRCC, sunitinib (333)	Hypertension	*CYP3A4* rs4646437	2.4 (1.1–5.2)	0.021	No
Garcia-Donas [19]	mRCC, sunitinib (84)	Toxicity-related DR	*CYP3A5* rs776746	3.75 (1.67–8.41)	0.022	Yes
Diekstra [11]	mRCC, sunitinib (333)	Hypertension	*CYP3A5* rs776746	4.70 (1.47–15.0)	0.009	Yes
		Toxicity-related DR		2.04 (1.04–4.00)	0.039	Yes
Van Erp [12]	mRCC, sunitinib (219)	Hand-foot syndrome	*ABCB1* rs1045642/ rs1128503/ rs2032582 haplotype	0.39 (0.16–0.94)	0.035	Yes
Beuselinck [30]	mRCC, sunitinib (96)	Median time to DR	*ABCB1* rs1128503	2.278 (1.07–4.82)	0.031	No
			ABCB1 rs2032582	2.106 (1.01–4.37)	0.046	No
Garcia-Donas [19]	cc-mRCC, sunitinib (101)	Hypertension	*ABCB1* rs1128503 *ABCB1* rs2032582	0.41 (0.20–0.81) 0·42 (0·21–0·84)	0.011 0.014	No
Diekstra [11]	mRCC, sunitinib (333)	Mucosal inflammation	*ABCB1* rs1128503/ rs2032582	0.19 (0.04–0.83)	0.028	Yes
		Toxicity grade >2	*ABCB1* rs1045642		0.04	No

SNP = single-nucleotide polymorphism; OR = odds ratio; CI = confidence interval; mRCC = metastatic renal cell carcinoma; cc = clear cell; DR = dose reduction