



Universiteit
Leiden
The Netherlands

Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: a meta-analysis

Liu, X.Y.; Fiocco, M.; Swen, J.J.; Guchelaar, H.J.

Citation

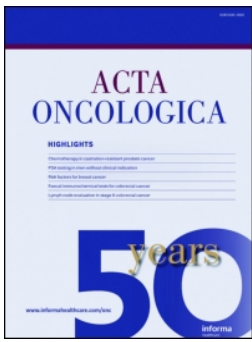
Liu, X. Y., Fiocco, M., Swen, J. J., & Guchelaar, H. J. (2017). Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: a meta-analysis. *Acta Oncologica*, 56(4), 582-589. doi:10.1080/0284186X.2016.1265666

Version: Not Applicable (or Unknown)

License: [Leiden University Non-exclusive license](#)

Downloaded from: <https://hdl.handle.net/1887/114718>

Note: To cite this publication please use the final published version (if applicable).



Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: a meta-analysis

Xiaoyan Liu, Marta Fiocco, Jesse J. Swen & Henk-Jan Guchelaar

To cite this article: Xiaoyan Liu, Marta Fiocco, Jesse J. Swen & Henk-Jan Guchelaar (2017) Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: a meta-analysis, Acta Oncologica, 56:4, 582-589, DOI: 10.1080/0284186X.2016.1265666

To link to this article: <https://doi.org/10.1080/0284186X.2016.1265666>



© 2016 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



[View supplementary material](#)



Published online: 07 Dec 2016.



[Submit your article to this journal](#)



Article views: 1198



[View related articles](#)



[View Crossmark data](#)



Citing articles: 14 [View citing articles](#)

Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: a meta-analysis

Xiaoyan Liu^{a,b}, Marta Fiocco^c, Jesse J. Swen^a and Henk-Jan Guchelaar^a

^aDepartment of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands; ^bInstitute of Clinical Pharmacology, Qilu Hospital of Shandong University, Jinan, China; ^cDepartment of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

Background: An increasing number of studies have reported ethnic differences in sunitinib outcome in metastatic renal cell carcinoma (mRCC) patients. However, a comprehensive analysis is still lacking. Therefore, we systematically collected available published data and performed a meta-analysis to compare sunitinib efficacy and toxicity in Asian and Caucasian mRCC patients.

Methods: Data were extracted from published results from clinical trials, expanded access program and real-world clinical practice. Progression-free survival (or time to tumor progression), overall survival, objective response rate and adverse events were used as endpoints to evaluate the differences of sunitinib outcome between the two ethnicities. For adverse events, we focused the following clinically relevant side effects: diarrhea, fatigue, mucositis/stomatitis, hand-foot syndrome, hypertension, leukopenia, neutropenia and thrombocytopenia.

Results: A total of 33 publications including 9977 patients were available for meta-analysis. The efficacy of sunitinib in Asian patients was similar to that in Caucasian patients. However, Asian patients showed a higher incidence of all grades toxicity of hand-foot syndrome, > grade 2 fatigue, > grade 2 hand-foot syndrome and > grade 2 thrombocytopenia.

Conclusion: Ethnic differences in adverse events of sunitinib in mRCC patients existed and dose adjustment in Asian patients may be considered.

ARTICLE HISTORY


Received 18 August 2016
Revised 18 November 2016
Accepted 22 November 2016


Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for nearly 2% of adult malignancies. About 25–30% of patients have metastatic spread by the time they are diagnosed with RCC [1]. During the past two decades, the therapy for metastatic renal cell carcinoma (mRCC) has undergone a major evolution. Treatment strategies have changed from interleukin-2 and interferon-alpha to targeted therapy including tyrosine kinase inhibitors (TKIs, such as sorafenib, sunitinib, pazopanib, axitinib, cabozantinib and lenvatinib), mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus), and the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab. More recently, a novel immunotherapeutic drug, nivolumab, has been added to the armamentarium of drugs to treat mRCC.

Sunitinib, an oral TKI, is primarily metabolized by cytochrome P450 (CYP) 3A4 into an active metabolite, SU12662. It received accelerated approval in January 2006 by the Food and Drug Administration (FDA) for the treatment of mRCC. The US approval of sunitinib was based on two single-arm, multicenter studies of single sunitinib treatment in mRCC. Both trials were conducted in the US, and the percentage of

Caucasian patients in these studies was 94% and 86%, respectively. In the two studies, sunitinib-treated patients presented an objective response rate of 25.5% (95% CI 17.5–34.9%) and 36.5% (95% CI 24.7–49.6%) [2]. Subsequently, the European Medicines Agency approved sunitinib for RCC in 2007, followed by approval for treatment of RCC in Japan and China in 2008. Sunitinib has become the first-line treatment for mRCC patients in the US, Europe, Australia, Japan, South Korea and Taiwan. Due to the strict reimbursement policies in some Asian countries, sunitinib has so far not yet been widely used as first-line treatment option for mRCC patients [3].

Generally, drug trials for market approval are conducted in western countries first and evaluations in other ethnicities are performed subsequently. It is well known that for certain drugs efficacy and toxicity vary greatly among different ethnicities. One example is that, in 2005, the FDA approved the first race-based drug BiDil for the treatment of heart failure in black patients [4]. Moreover, it was reported that of 167 drugs approved by the FDA between 2008 and 2013, 21% reported some racial or ethnic differences in pharmacokinetics, safety, efficacy or pharmacogenomics in the label [5].

CONTACT Henk-Jan Guchelaar  H.J.Guchelaar@lumc.nl  Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Albinusdreef 2, Leiden, 2333ZA, The Netherlands

 Supplemental data for this article can be accessed [here](#).

© 2016 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

Ample examples of ethnic differences in drug response in the field of oncology are known. Ye et al. [6] compared sorafenib outcomes between Chinese and Caucasian RCC patients. Sorafenib appeared to be more effective in patients of Chinese ethnicity than in Caucasian patients. However, Chinese patients more frequently experienced hand-foot syndrome. Similarly, ethnic differences in the frequency of axitinib-related hand-foot syndrome were found between Japanese and Caucasian patients [7].

Until now, differences in sunitinib outcomes among ethnicities have been investigated in two studies. In 2013, Motzer et al. [8] retrospectively collected data from six clinical trials and reported that there was no significant difference in survival in Caucasian (n=884) versus Asian mRCC patients (n=70). However, several sunitinib-induced adverse events such as hand-foot syndrome occurred significantly more often in Asian patients compared to Caucasian patients (70% vs. 28%, $p < 0.001$). In addition, evidence from a global expanded access program (EAP) with 4371 mRCC patients reported a comparable sunitinib efficacy between Asian (n=325) and non-Asian patients (n=4046), and major differences in the incidence of all grade stomatitis (39% vs. 26%, Asian and non-Asian patients, respectively), hand-foot syndrome (39% vs. 23%), asthenia (12% vs. 22%), and skin discoloration (25% vs. 9%) [9]. Recently, a prospective, post-marketing study, including 1689 Japanese patients with mRCC, was performed to investigate sunitinib efficacy and toxicity in real-world clinical practice. Hand-foot syndrome as well as thrombocytopenia was observed at higher frequencies and with greater severity in Japanese as compared with Caucasian patients [10].

Although several studies investigated ethnic differences in sunitinib efficacy and toxicity, no comprehensive analysis is available at present. Therefore, we systematically collected available published data and performed a meta-analysis to compare sunitinib efficacy as well as toxicity in Asian and Caucasian mRCC patients.

Materials and methods

Systematic literature search strategy and selection process

A systematic search for publications archived in MEDLINE, EMBASE and Web of Science prior to 9 October 2015 was conducted. A search syntax was compiled by combining 'renal cell carcinoma' AND 'sunitinib' AND 'ethnicity'. Various synonyms and related terms for all subjects were used (the search syntax is supplied in Supplementary document 1). Duplicate articles were removed after manual curation. Initially, articles were scanned by title and abstract. Meeting abstracts, case reports, reviews and meta-analyses were excluded. Reference lists were carefully evaluated to identify additional relevant papers. Only full-text articles published in English, reporting on efficacy and toxicity in single sunitinib treatment were included. The treatment had to consist of an initial regimen of 50 mg daily dose (4-week on/2-week off) or continuous 37.5 daily regimen in mRCC patients.

Endpoints and data extraction

The primary endpoints of this meta-analysis were progression-free survival (PFS), objective response rate (ORR, only complete and partial response have been considered) and adverse events (AEs) in mRCC patients. Overall survival (OS) was regarded as secondary endpoint as PFS more closely reflects drug effects.

From the included articles, the following data were collected: first author, year of publication, sample size, median age, percentage of males, ethnicity (or country, region), sunitinib initial regimen (50 mg daily dose with 4/2 schedule or continuous 37.5 mg daily dose), tumor histology, study setting (clinical trial, EAP, real-world clinical practice), prior treatment percentage, ORR, median OS, median PFS (or time to tumor progression if PFS was not reported), follow-up period, and incidence of AEs. Based on the existing literature [11], we focused on the following clinically relevant AEs, i.e., diarrhea, fatigue, mucositis/stomatitis, hand-foot syndrome, hypertension, leukopenia, neutropenia and thrombocytopenia. AEs higher than grade 2 as well as all grades of AEs were obtained.

Statistical analysis

Meta-analysis was performed based on the survival outcomes coming from the included studies. Individual patient data were reconstructed from the estimated PFS and OS probabilities. Data in each study consisted of PFS or OS and probabilities every five months for the first two or three years after treatment. Details concerning the reconstruction of the data were described in the Appendix (Supplementary document 2). Further technical details were discussed in Fiocco et al. [12,13]. A multivariate random-effects model for a joint analysis of survival proportions reported at different times in the individual studies was used to combine all available information in each article included in the meta-analysis on the endpoint of PFS and OS. Moreover, a series of separate meta-analysis on toxicity data were performed for Caucasian and Asian patients as well. A random effect model was used to pool specific proportion in order to estimate an overall proportion and its associated confidence intervals. Inverse variance method which gives more weight to larger trials was used to pool outcomes for different studies [14]. All statistical analyses were performed in R environments version 2.18 (<http://cran.rproject.org/>).

Results

Search results

Our systematic search identified 1514 publications. After selecting by title, abstract, inclusion and exclusion criteria, 30 articles remained. Manual curation of reference lists identified three additional papers [15–17]. Finally, a total of 33 publications, including 9977 patients, were available for meta-analyses [2,8–10,15–43]. Of these 33 publications, 19 were eligible for survival analyses, 28 for AEs analysis and 20 for ORR.

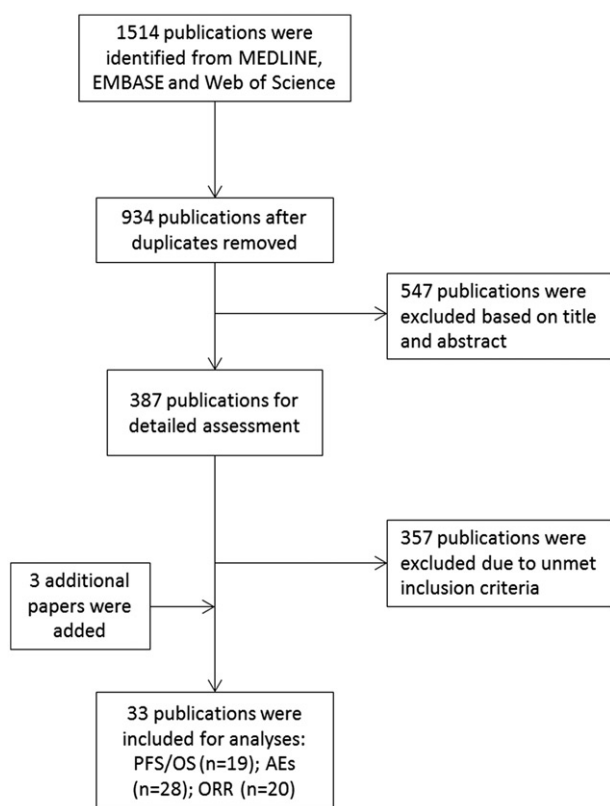


Figure 1. Flowchart of study selection. The original search on the 9 October 2015 resulted in a total of 1514 publications. Three additional publications were included based on manual curation of reference lists. In total 1484 publications were excluded due to duplication ($n = 580$), title and abstract ($n = 547$), data were not from single sunitinib treatment or included patients with multiple tumor types ($n = 349$), dosing regimen was not 50 mg 4/2 schedule or continuous 37.5 mg daily ($n = 2$), duplicate cohort ($n = 3$), only elderly or renal insufficient or sunitinib treatment more than 1 year patients were included ($n = 3$). Finally, 33 publications were included in our paper.

Figure 1 represents a flowchart on the study selection process.

Study characteristics

All studies included were published between 2006 and 2015 (details were provided in Supplementary Table 1). A total of 21 publications included patients from real-world clinical practice ($n = 3869$), another 11 publications included 1737 patients enrolled in clinical trials, and a large study included 4371 patients who participated in an EAP. In the subgroup of clinical trials and the EAP, Caucasian patients represent $>90\%$ of the patients. The median age of the patients per study ranged from 55 to 66 years. Of these patients, more than 70% were males.

Meta-analysis of sunitinib outcomes between Caucasian and Asian mRCC patients

The results of the meta-analysis for all grade toxicities in Asian and Caucasian mRCC patients were displayed in **Figure 2**. The incidence of hand-foot syndrome in Asian patients (52%, 95% CI 45–60%) was found to be two times higher than that in Caucasian patients (24%, 95% CI 19–29%). Asian and Caucasian patients had a similar

incidence of toxicity other than hand-foot syndrome. Pooled incidence of toxicities higher than grade 2 was shown in **Figure 3**. Asian patients showed a higher percentage of $>$ grade 2 fatigue, hand-foot syndrome and thrombocytopenia of 17 (95% CI 11–13)%, 13 (95% CI 9–17)% and 25 (95% CI 18–32)%, in comparison to Caucasian patients for whom the results were 8 (95% CI 6–9)%, 5 (95% CI 3–7)% and 6 (95% CI 2–10)%, respectively. There were no significant differences of other $>$ grade 2 toxicities.

Figure 4 displayed the estimated pooled mean survival for PFS and OS in Asian and Caucasian patients, respectively. No significant difference was found between Asian and Caucasian patients. For PFS, the hazard ratio for Caucasian patients was 0.900 (95% CI 0.018–1.345, p -value = 0.280). For OS, the hazard ratio was 1.330 (95% CI 0.912–1.330, p -value = 0.314).

Results for ORR were shown by ethnicity and stratified by setting (clinical trial, EAP and real-world clinical practice); the results were displayed in **Figure 5**. ORR for all Asian patients ranged from 14% to 52.4%, and 14% to 47% for Caucasian patients. No ORR data could be found in publications including Asian patients from clinical trials.

An overview of primary and secondary outcome parameters at individual study level was shown in Supplementary Tables 2–4.

Discussion

In the current meta-analysis, we systematically collected available data to compare sunitinib outcomes between Asian and Caucasian mRCC patients. Our results showed that the efficacy of sunitinib in mRCC patients from Caucasian and Asian origin was similar. However, a higher incidence of all grades hand-foot syndrome, $>$ grade 2 fatigue, $>$ grade 2 hand-foot syndrome and $>$ grade 2 thrombocytopenia was observed in Asian patients. In addition, we compared the ORR among three patient settings. The range of ORR of patients from real-world clinical practice appeared to be larger than that from the clinical trial setting. However, the difference of ORR is not as large as we had expected, because the patients from real-world clinical practice usually were more heterogeneous than those enrolled in a clinical trial.

A potential explanation for the observed higher risk of toxicity in Asian patients may be increased drug exposure. As to the pharmacokinetics of sunitinib, Houk et al. assessed the population pharmacokinetics of sunitinib and SU12662 including patients with mRCC, gastrointestinal stromal tumor and other solid tumors. It was shown that the drug exposure (indicated as AUC) and the maximal plasma drug concentration (C_{max}) for both sunitinib and SU12662 in Asian patients were about 15% higher compared to other ethnic groups [44]. In addition, Nagata et al. [45] reported that the total trough level of sunitinib in six Japanese RCC patients using 50mg daily 4/2 schedule was higher than 100 ng/ml, whereas the average concentration of total sunitinib in Caucasian male patients (body weight: 77 kg, 50 mg daily dose) stated by Houk et al. [44] was 30–90 ng/ml. Of note, in the studies

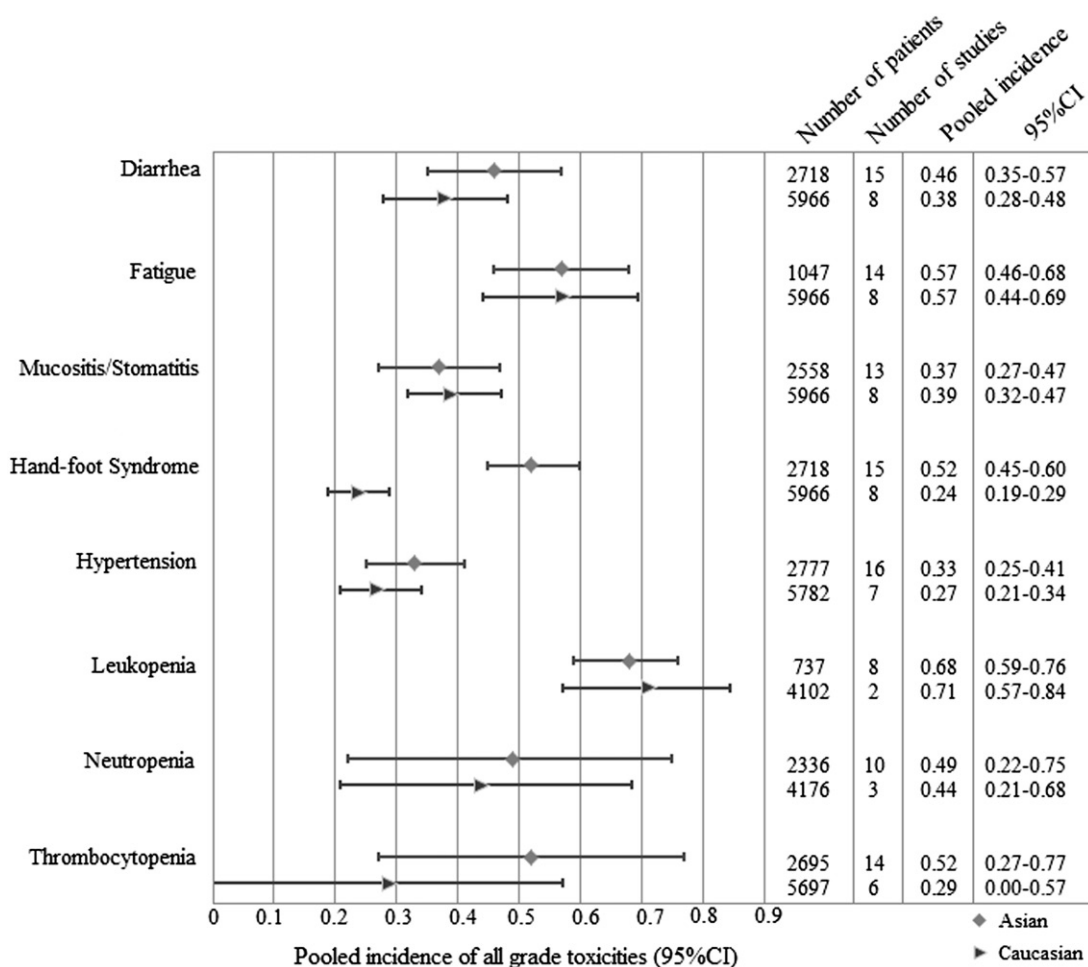


Figure 2. Pooled incidence of all grade toxicities.

included in our meta-analysis, sunitinib was administrated as a standard daily dose of 50 mg in a 4-week on/2-week off schedule. Compared to the Caucasian population, Asian people in general have a relatively lower body surface area (BSA), and as a result drug exposure in Asian patients may be higher after a standard dose. However, no or only a relatively small effect of BSA on sunitinib pharmacokinetics was identified in both Caucasian [44] and Japanese patients [46]. In contrast, the lean body mass (LBM) has recently been identified to be related with sunitinib and SU12662 exposure in 92 patients with solid tumors. The authors reported that patients with a lower LBM had a higher sunitinib and SU12662 exposure [47]. Compared to Caucasians, Asian patients in general have a lower LBM [48], and therefore might have higher exposure of sunitinib and SU12662.

The ethnic differences in sunitinib pharmacokinetics and toxicity incidence may at least in part be explained by the diversity in allele frequencies of variants in genes encoding enzymes and transporters involved in drug absorption and metabolism. The association of sunitinib-induced toxicities with pharmacogenetic determinants was studied by Kim et al. in 65 Korean mRCC patients [49]. Compared to C-allele carriers, patients with the AA variant genotype of the drug transporter *ABCG2* rs2231142 had an increased risk for grade 3 or 4 thrombocytopenia, neutropenia and hand-foot syndrome [49]. As to the relation of this SNP with

pharmacokinetic parameters, Mizuno et al. clarified the effect of the *ABCG2* rs2231142 genotype in 19 Japanese RCC patients [50,51]. The clearance/F estimated in A-allele carriers of rs2231142 was approximately 50% of that in patients with CC genotype. Compared to CC-genotype patients, the dose-adjusted AUC_{0-24} of sunitinib was significantly higher in A-allele carriers. It was shown that the steady-state plasma concentrations in A-allele carriers on the daily dose of 25 mg were in the same concentration range (60–80 ng/ml) as seen in CC-genotype patients on the standard 50 mg daily dose. In another cohort with 66 mRCC patients from France, the association of *ABCG2* rs2231142 with sunitinib and SU12662 has been confirmed [47]. Considering that the variant allele A is more common in Japanese, Korean and Chinese (about 30%) than in Caucasian (10%) [52], the ethnic difference in minor allele frequency (MAF) of this SNP might be an underlying cause of the higher sunitinib toxicity reported in Asian patients. In addition, the genetic variant rs776746G>A in the drug-metabolizing enzyme *CYP3A5* is associated with the defective *CYP3A5* expression, resulting in a decreased conversion of sunitinib into SU12662. It has been reported that sunitinib exhibited more dermatological toxicities (among which hand-foot syndrome) compared to SU12662 [53]. Garcia-Donas et al. reported the association of *CYP3A5**3 with toxicity-related dose reduction in 101 Spanish mRCC patients [54]. *CYP3A5**3 is common in Asian (34%), but rare in

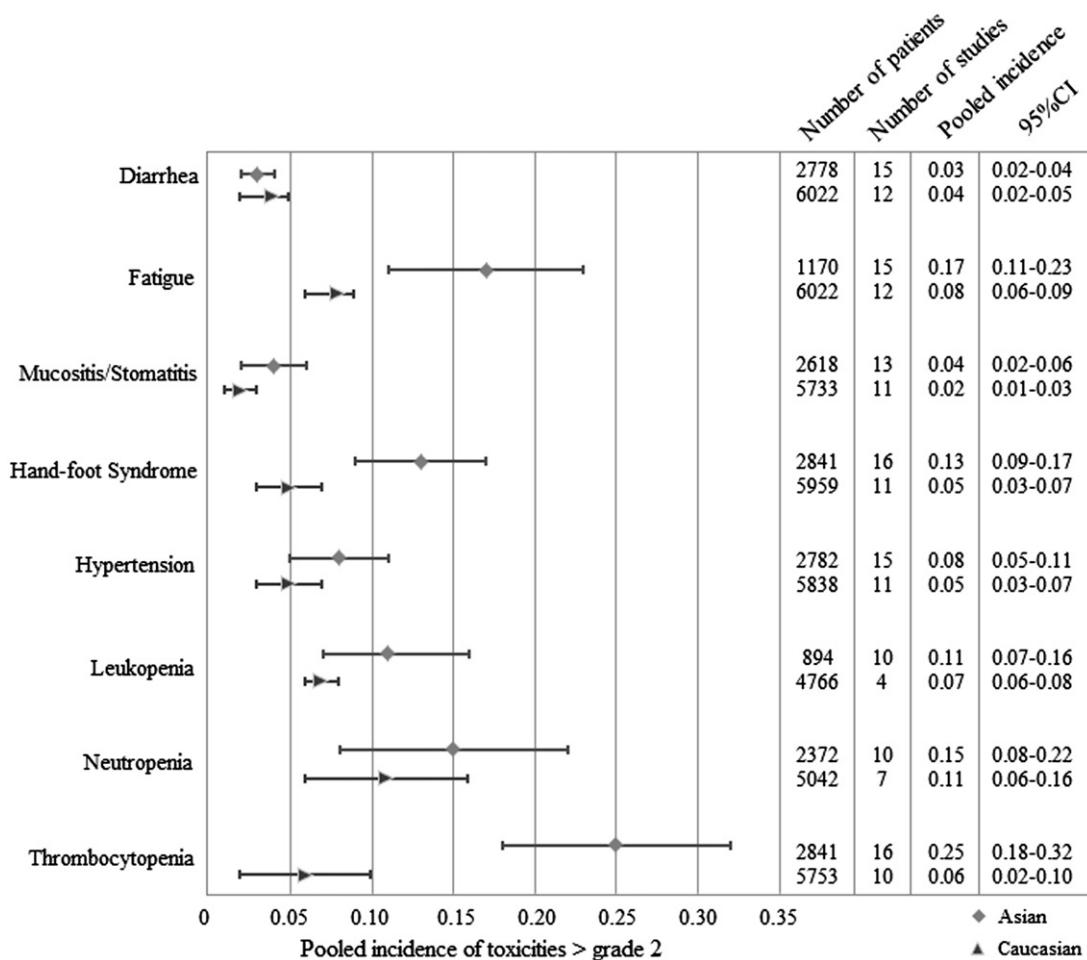


Figure 3. Pooled incidence of higher than grade 2 toxicities.

Caucasians (4%), implying the potential effect of this SNP on the different incidence of hand-foot syndrome between two ethnic groups. It has been assumed that *CYP3A5**3 is linked with higher sunitinib exposure. The potential association has been explored in Caucasian [55] and Asian mRCC patients [56]. However, no clear correlations between *CYP3A5**3 and sunitinib exposure were observed in either population.

Moreover, a recent retrospective study in 114 Caucasian patients with sunitinib treatment showed that *CYP3A4**22 (rs35599367 C > T) was associated with decreased sunitinib clearance [55]. It has been reported that activity of *CYP3A4* enzyme is particularly sensitive to dietary effects [57]. Although the potential effect of food on sunitinib pharmacokinetics was not supported by the phase I study in healthy subjects, in which no difference of sunitinib and SU12662 pharmacokinetics was found between patients with single dose of sunitinib after either 10-hour fast or a high-fat meal, the effect of long-term cooking habit, such as the frequently used *CYP3A4*-inhibiting spices [58], could not be ignored.

The effect sizes of above-mentioned factors are relatively small compared to the inter-individual variability of pharmacokinetic characteristics of 32.2% and 42.9% in clearance of sunitinib and SU12662 reported by Diekstra et al. [55], and even higher variability published by Houk et al. (37.9% and 52.2%, respectively) [44].

Besides the comparison between Asian and Caucasian patients, an interesting subgroup analysis is the comparison between Asian patients from Asian sites (Asian-A) and Asian patients from non-Asian sites (Asian-O) performed by Lee et al. [9]. It was shown that Asian-O patients had lower incidence of toxicity compared to Asian-A, but had a similar incidence of toxicity as non-Asian patients. This observation points towards the direction of diet and body weight being a major determinant of sunitinib toxicity. Indeed, Park et al. reported that Asians living in the US have a comparable amount of visceral fat to that of European Americans [59]. Moreover, a meta-analysis showed that visceral fat in Japanese population was significantly lower than that in Caucasians [60]. Obviously, visceral fat may modify drug distribution and thus decrease drug exposure in the tumor [61].

In a real-world clinical setting, reimbursement policies in different countries may indirectly contribute to ethnic differences of sunitinib efficacy and toxicity. For example, even though five agents (sorafenib, sunitinib, everolimus, interferon-alpha and interleukin-2) are currently approved by Chinese Food and Drug Administration for mRCC treatment, reimbursement is only available for interferon-alpha and interleukin-2 [62]. This may imply that sunitinib is more frequently used as a second-line treatment of advanced disease patients in some Asian countries compared to Caucasian countries. However, this potential effect does not play a role

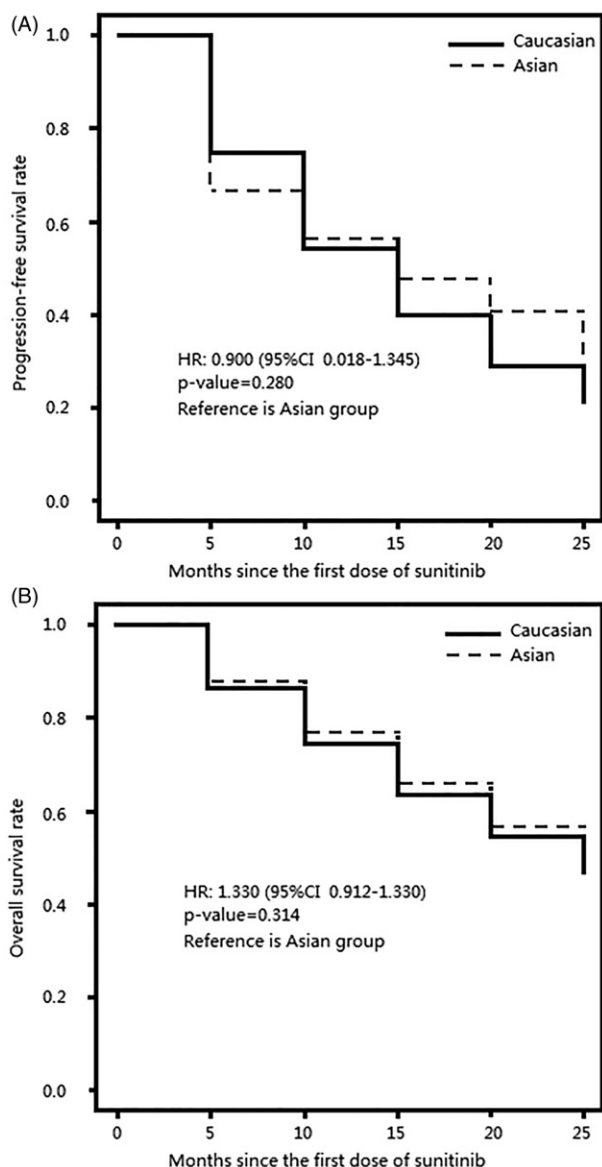


Figure 4. Pooled progression-free survival (A) and overall survival (B).

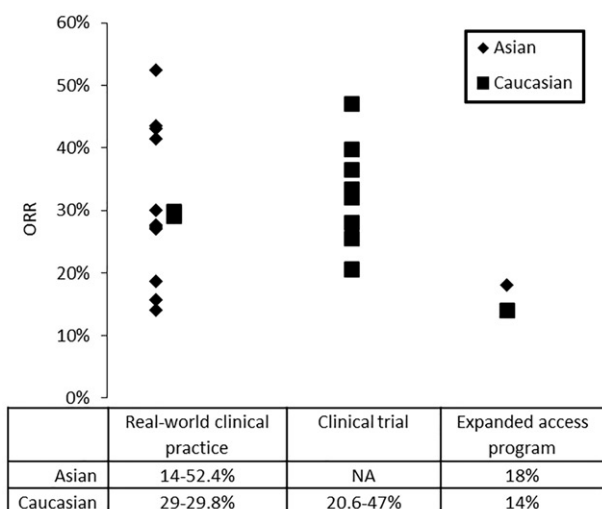


Figure 5. Objective response rate (ORR) stratified by setting. NA: not available.

in our meta-analysis, as no differences in the percentage of patients with prior treatment from Asian or Caucasian countries was observed (Supplementary Table 1).

The present meta-analysis pooled all available data from three different patient settings (clinical trial, EAP and real-world clinical practice). Due to the strict and homogeneous patient selection criteria, drug effects in clinical trials may not be fully representative of real-world clinical practice and data from various types of drugs suggest the existence of a ‘trial effect’ [63]. Patients from EAP were those who were not eligible to participate in clinical trials due to exclusion criteria or were from countries where regulatory approval had not yet been granted. Therefore, the results from EAP may better reflect, to some extent, the results found in real-world clinical practice. Subgroup analyses could give some insight into inter-setting differences of sunitinib efficacy and toxicity between ethnicities, but the data available at present do not allow for performing such subgroup analyses. However, the comparison of sunitinib efficacy between clinical trial participants and a matched cohort of non-participants was explored by Keizman et al., but no significant difference was observed [63].

Available data indicate that Asian patients more frequently need a toxicity-related dose reduction or discontinuation compared to Caucasian patients with 35–76% versus 24–32%, respectively [20]. It has been suggested that Asian patients should start their treatment with a lower initial sunitinib dose. This approach was evaluated in a prospective study comparing the conventional dose regimen (50 mg daily, 4-week on/2-week off) with an attenuated dose regimen (37.5 mg daily, 4-week on/2-week off) in 160 Singapore mRCC patients. The results showed that patients with attenuated dose regimen had comparable PFS and OS, but had significantly lower incidence of toxicity compared to those with conventional dose regimen. From this study, it seems that Asian patients, with a reduced initial dose, have reached a balance of minimum toxicity and maximum efficacy [20].

The authors would like to point out that this study has some limitations that ought to be considered. There is a lack of standard definition of Asian and Caucasian origin, and it is difficult to designate a multiracial identity. Indeed, the majority of included publications did not report detailed information of ethnicity. Even though we contacted the authors of included studies, no full ethnic data appeared to be available. Therefore, we decided to regard the patients enrolled in Asian countries as Asian and patients enrolled in European and American studies as Caucasian, except when the ethnic data were presented otherwise. Moreover, although sunitinib is a standard-of-care treatment in clear cell RCC, it is acknowledged that efficacy is dependent of histological tumor type [64]. Therefore, we excluded two papers [25,36] with a high percentage of non-clear cell RCC patients, from efficacy analysis.

In conclusion, at a standard dose, Asian patients more frequently experience sunitinib-induced toxicity, such as hand-foot syndrome, fatigue and thrombocytopenia compared to Caucasian patients. No significant ethnic difference of sunitinib efficacy in mRCC patients was found in the present study.

Therefore, dose adjustment in Asian patients may be considered.

Acknowledgments

We would like to especially thank Jan Schoones, librarian at Leiden University Medical Center, for helping the authors with the systematic literature search.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

Xiaoyan Liu is supported by the Chinese Scholarship Council [No. 201406220186].

References

- [1] Naito S, Tomita Y, Rha SY, et al. Kidney cancer working group report. *Jpn J Clin Oncol*. 2010;40:i51–i56.
- [2] Goodman VL, Rock EP, Dagher R, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res*. 2007;13:1367–1373.
- [3] Ye D, Eto M, Chung JS, et al. Use of targeted therapies for advanced renal cell carcinoma in the Asia-Pacific region: opinion statement from China, Japan, Taiwan, Korea, and Australia. *Clin Genitourin Cancer*. 2014;12:225–233.
- [4] Temple R, Stockbridge NL. BiDil for heart failure in black patients: the U.S. Food and Drug Administration perspective. *Ann Intern Med*. 2007;146:57–62.
- [5] Ramamoorthy A, Pacanowski M, Bull J, et al. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. *Clin Pharmacol Ther*. 2015;97:263–273.
- [6] Ye DW, Zhang HL. Critical appraisal of sorafenib in the treatment of Chinese patients with renal cell carcinoma. *Onco Targets Ther*. 2014;7:925–935.
- [7] Chen Y, Suzuki A, Tortorici MA, et al. Axitinib plasma pharmacokinetics and ethnic differences. *Invest New Drugs*. 2015;33:521–532.
- [8] Motzer RJ, Escudier B, Bukowski R, et al. Prognostic factors for survival in 1059 patients treated with sunitinib for metastatic renal cell carcinoma. *Br J Cancer*. 2013;108:2470–2477.
- [9] Lee SH, Bang YJ, Mainwaring P, et al. Sunitinib in metastatic renal cell carcinoma: an ethnic Asian subpopulation analysis for safety and efficacy. *Asia Pac J Clin Oncol*. 2014;10:237–245.
- [10] Akaza H, Naito S, Ueno N, et al. Real-world use of sunitinib in Japanese patients with advanced renal cell carcinoma: efficacy, safety and biomarker analyses in 1689 consecutive patients. *Jpn J Clin Oncol*. 2015;45:576–583.
- [11] Kollmannsberger C, Soulieres D, Wong R, et al. Sunitinib therapy for metastatic renal cell carcinoma: recommendations for management of side effects. *Can Urol Assoc J*. 2007;1:S41–S54. Suppl 2).
- [12] Fiocco M, Putter H, van Houwelingen JC. Meta-analysis of pairs of survival curves under heterogeneity: a Poisson correlated gamma-frailty approach. *Stat Med*. 2009;28:3782–3797.
- [13] Fiocco M, Stijnen T, Putter H. Meta-analysis of time-to-event outcomes using a hazard-based approach: Comparison with other models, robustness and meta-regression. *Comput Stat Data Anal*. 2012;56:1028–1037.
- [14] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
- [15] Motzer RJ, Hutson TE, Olsen MR, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. *J Clin Oncol*. 2012;30:1371–1377.
- [16] Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24:16–24.
- [17] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115–124.
- [18] Pan X, Huang H, Huang Y, et al. Sunitinib dosing schedule 2/1 improves tolerability, efficacy, and health-related quality of life in Chinese patients with metastatic renal cell carcinoma. *Urol Oncol*. 2015;33:268.e9–268.e15.
- [19] Miyake H, Harada K, Miyazaki A, et al. Improved health-related quality of life of patients with metastatic renal cell carcinoma treated with a 2 weeks on and 1 week off schedule of sunitinib. *Med Oncol*. 2015;32:78. doi: 10.1007/s12032-015-0528-8.
- [20] Tan HS, Li H, Hong YW, et al. Efficacy and safety of an attenuated-dose sunitinib regimen in metastatic renal cell carcinoma: results from a prospective registry in Singapore. *Clin Genitourin Cancer*. 2015;13:e285–e295.
- [21] Ohzeki T, Fukasawa S, Komaru A, et al. Efficacy of traditional and alternative sunitinib treatment schedules in Japanese patients with metastatic renal cell carcinoma. *Int J Urol*. 2014;21:1065–1068.
- [22] Miyake H, Miyazaki A, Harada K, et al. Assessment of efficacy, safety and quality of life of 110 patients treated with sunitinib as first-line therapy for metastatic renal cell carcinoma: experience in real-world clinical practice in Japan. *Med Oncol*. 2014;31:978. doi: 10.1007/s12032-014-0978-4.
- [23] He Z, Guo G, Zhang C, et al. Efficacy of sunitinib in patients with metastatic renal cell carcinoma: initial experience in two Chinese centers. *Chin Med J (Engl)*. 2014;127:1450–1453.
- [24] Krishna VM, Noronha V, Prabhash K, et al. Sunitinib in metastatic renal cell carcinoma: a single-center experience. *Indian J Cancer*. 2013;50:268–273.
- [25] Kawashima A, Tsujimura A, Takayama H, et al. Importance of continuing therapy and maintaining one-month relative dose intensity in sunitinib therapy for metastatic renal cell carcinoma. *Med Oncol*. 2012;29:3298–3305.
- [26] Yuasa T, Tsuchiya N, Urakami S, et al. Clinical efficacy and prognostic factors for overall survival in Japanese patients with metastatic renal cell cancer treated with sunitinib. *BJU Int*. 2012;109:1349–1354.
- [27] Hwang E, Lee HJ, Sul CK, et al. Efficacy and safety of sunitinib on metastatic renal cell carcinoma: a single-institution experience. *Korean J Urol*. 2010;51:450–455.
- [28] Lee JH, Chang SG, Jeon SH, et al. Comparative analysis between immunochemotherapy and target therapy for metastatic renal cell carcinoma: overview of treatment-related adverse events and the Dropout Rate in Korea. *Korean J Urol*. 2010;51:379–385.
- [29] Yoo C, Kim JE, Lee JL, et al. The efficacy and safety of sunitinib in Korean patients with advanced renal cell carcinoma: toxicity and treatment patterns in clinical practice from a global medical chart review. *Int J Oncol*. 2010;40:980–985.
- [30] Hong MH, Kim HS, Kim C, et al. Treatment outcomes of sunitinib treatment in advanced renal cell carcinoma patients: a single cancer center experience in Korea. *Cancer Res Treat*. 2009;41:67–72.
- [31] Oh WK, McDermott D, Porta C, et al. Angiogenesis inhibitor therapies for advanced renal cell carcinoma: toxicity and treatment patterns in clinical practice from a global medical chart review. *Int J Oncol*. 2014;44:5–16.
- [32] Yildiz I, Sen F, Basaran M, et al. Response rates and adverse effects of continuous once-daily sunitinib in patients with advanced renal cell carcinoma: a single-center study in Turkey. *Jpn J Clin Oncol*. 2011;41:1380–1387.
- [33] Porta C, Levy A, Hawkins R, et al. Impact of adverse events, treatment modifications, and dose intensity on survival among

- patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. *Cancer Med.* 2014;3:1517–1526.
- [34] Feinberg BA, Jolly P, Wang ST, et al. Safety and treatment patterns of angiogenesis inhibitors in patients with metastatic renal cell carcinoma: evidence from US community oncology clinics. *Med Oncol.* 2012;29:786–794.
- [35] Porta C, Paglino C, Imarisio I, et al. Safety and treatment patterns of multikinase inhibitors in patients with metastatic renal cell carcinoma at a tertiary oncology center in Italy. *BMC Cancer.* 2011;11:105. doi: 10.1186/1471-2407-11-105.
- [36] Ansari J, Fatima A, Fernando K, et al. Sunitinib in patients with metastatic renal cell carcinoma: Birmingham experience. *Oncol Rep.* 2010;24:507–510.
- [37] Sabatier R, Eymard JC, Walz J, et al. Could thyroid dysfunction influence outcome in sunitinib-treated metastatic renal cell carcinoma? *Ann Oncol.* 2012;23:714–721.
- [38] Zhao J, Zhu Y, Zhang C, et al. Sorafenib or sunitinib as postoperative adjuvant therapy for Chinese patients with locally advanced clear cell renal cell carcinoma at high risk for disease recurrence. *Urol Oncol.* 2013;31:1800–1805.
- [39] Tomita Y, Shinohara N, Yuasa T, et al. Overall survival and updated results from a phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma. *Jpn J Clin Oncol.* 2010;40:1166–1172.
- [40] Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009;27:3584–3590.
- [41] Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA.* 2006;295:2516–2524.
- [42] Escudier B, Roigas J, Gillessen S, et al. Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. *J Clin Oncol.* 2009;27:4068–4075.
- [43] Motzer RJ, Michaelson MD, Rosenberg J, et al. Sunitinib efficacy against advanced renal cell carcinoma. *J Urol.* 2007;178:1883–1887.
- [44] Houk BE, Bello CL, Kang D, et al. A population pharmacokinetic meta-analysis of sunitinib malate (SU11248) and its primary metabolite (SU12662) in healthy volunteers and oncology patients. *Clin Cancer Res.* 2009;15:2497–2506.
- [45] Nagata M, Ishiwata Y, Takahashi Y, et al. Pharmacokinetic-pharmacodynamic analysis of sunitinib-induced thrombocytopenia in Japanese patients with renal cell carcinoma. *Biol Pharm Bull.* 2015;38:402–410.
- [46] Uemura H, Shinohara N, Yuasa T, et al. A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into the treatment, efficacy and safety. *Jpn J Clin Oncol.* 2010;40:194–202.
- [47] Narjoz C, Cessot A, Thomas-Schoemann A, et al. Role of the lean body mass and of pharmacogenetic variants on the pharmacokinetics and pharmacodynamics of sunitinib in cancer patients. *Invest New Drugs.* 2015;33:257–268.
- [48] Lear SA, Kohli S, Bondy GP, et al. Ethnic variation in fat and lean body mass and the association with insulin resistance. *J Clin Endocrinol Metab.* 2009;94:4696–4702.
- [49] Kim HR, Park HS, Kwon WS, et al. Pharmacogenetic determinants associated with sunitinib-induced toxicity and ethnic difference in Korean metastatic renal cell carcinoma patients. *Cancer Chemother Pharmacol.* 2013;72:825–835.
- [50] Mizuno T, Fukudo M, Fukuda T, et al. The effect of ABCG2 genotype on the population pharmacokinetics of sunitinib in patients with renal cell carcinoma. *Ther Drug Monit.* 2014;36:310–316.
- [51] Mizuno T, Fukudo M, Terada T, et al. Impact of genetic variation in breast cancer resistance protein (BCRP/ABCG2) on sunitinib pharmacokinetics. *Drug Metab Pharmacokin.* 2012;27:631–639.
- [52] Kim KA, Joo HJ, Park JY. ABCG2 polymorphisms, 34G>A and 421C>A in a Korean population: analysis and a comprehensive comparison with other populations. *J Clin Pharm Ther.* 2010;35:705–712.
- [53] Teo YL, Chong XJ, Chue XP, et al. Role of sunitinib and SU12662 on dermatological toxicities in metastatic renal cell carcinoma patients: *in vitro*, *in vivo*, and outcomes investigation. *Cancer Chemother Pharmacol.* 2014;73:381–388.
- [54] Garcia-Donas J, Esteban E, Leandro-García LJ, et al. Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. *Lancet Oncol.* 2011;12:1143–1150.
- [55] Diekstra MH, Klümpen HJ, Lolkema MP, et al. Association analysis of genetic polymorphisms in genes related to sunitinib pharmacokinetics, specifically clearance of sunitinib and SU12662. *Clin Pharmacol Ther.* 2014;96:81–89.
- [56] Teo YL, Wee HL, Chue XP, et al. Effect of the CYP3A5 and ABCB1 genotype on exposure, clinical response and manifestation of toxicities from sunitinib in Asian patients. *Pharmacogenom J.* 2016;16:47–53.
- [57] Harris RZ, Jang GR, Tsunoda S. Dietary effects on drug metabolism and transport. *Clin Pharmacokinet.* 2003;42:1071–1088.
- [58] Zhang W, Lim LY. Effects of spice constituents on P-glycoprotein-mediated transport and CYP3A4-mediated metabolism *in vitro*. *Drug Metab Dispos.* 2008;36:1283–1290.
- [59] Park YW, Allison DB, Heymsfield SB, et al. Larger amounts of visceral adipose tissue in Asian Americans. *Obes Res.* 2001;9:381–387.
- [60] Tanaka S, Horimai C, Katsukawa F. Ethnic differences in abdominal visceral fat accumulation between Japanese, African-Americans, and Caucasians: a meta-analysis. *Acta Diabetol.* 2003;40:5302–5304.
- [61] Nault JC, Pigneur F, Nelson AC, et al. Visceral fat area predicts survival in patients with advanced hepatocellular carcinoma treated with tyrosinekinase inhibitors. *Dig Liver Dis.* 2015;47:869–876.
- [62] Tan X, Liu Y, Hou J, et al. Targeted therapies for renal cell carcinoma in Chinese patients: focus on everolimus. *Onco Targets Ther.* 2015;8:313–321.
- [63] Keizman D, Rouvinov K, Sella A, et al. Is there a “Trial effect on outcome of patients with metastatic renal cell carcinoma treated with sunitinib?” *Cancer Res Treat.* 2016;48:281–287.
- [64] Sankin A, Hakimi A, Hsieh J, et al. Metastatic non-clear cell renal cell carcinoma: an evidence based review of current treatment strategies. *Front Oncol.* 2015;5:67. doi: 10.3389/fonc.2015.00067.