

Comparative efficacy and safety of sunitinib vs sorafenib in renal cell carcinoma

A systematic review and meta-analysis

Xiu-Lan Liu, MD^a, Hui-Ying Xue, MD^a, Qian Chu, PhD^b, Jin-Yu Liu, MD^{a,*}, Juan Li, MD^{a,*}

Abstract

To evaluate the safety and efficiency of sunitinib and sorafenib in the treatment of renal cell carcinoma (RCC).

Databases were searched up till February 28, 2018. Two reviewers independently assessed trials for eligibility, quality, and extracted relevant data. Results are expressed as risk ratio (RR) or hazard ratio (HR) with 95% confidence intervals (CI). Six studies including 3112 patients were accessed. Sorafenib group exhibited higher median progression-free survival (mPFS) compared to sunitinib group (MD, -1.30; 95% CI, -2.56 to -0.03), especially in the first-line treatment (MD, -1.33; 95% CI, -2.61 to -0.04). However, sunitinib significantly reduced the risk of progression-free survival (PFS) compared to sorafenib (HR, 0.71; 95% CI, 0.6–0.82). Sunitinib also significantly reduced risk of overall survival (OS) compared to sorafenib (HR, 0.79; 95% CI, 0.65–0.92), while median OS was similar in both groups (MD, -0.48; 95% CI, -3.40–2.43). With regards to safety, the risk of rash (RR, 0.31, 95% CI, 0.12–0.79) was greater in sunitinib than sorafenib group, while the risk of decreased appetite (RR 2.10, 95% CI: 1.33–3.30) and dehydration (RR 2.73, 95% CI: 1.14–6.56) was smaller in contrast.

Based on risk of PFS and OS, sunitinib was a better treatment option for RCC treatment while patients faced with severe skin reaction. And for those Asian patients classified under MSKCC moderate risk, whether in first or second-line treatment, had difficulty in feeding, sorafenib is a better choice for prolong mPFS.

Abbreviations: AEs = adverse events, CI = confidence intervals, HR = hazard ratio, IFN = interferon, IL = interleukin, mOS = median overall survival, mPFS = median progression-free survival, mRCC = metastatic RCC, OS = overall survival, PFS = progression-free survival, RCC = renal cell carcinoma, RR = risk ratio.

Keywords: efficiency, renal cell carcinoma, safety, sorafenib, sunitinib

1. Introduction

Renal cell carcinoma (RCC) is the most common malignant tumor in the clinical urinary system, originating from renal tubular epithelial cells. As the 8th most common cancer worldwide, RCC accounts for 23% of all adult malignancies

and causes approximately 140,000 deaths per year.^[1] The prognosis of RCC is highly dependent on stage. Surgical treatment is recognized as the first choice for most patients with RCC currently, leading to more than 70% 5-year relative survival rates. However, 25% of patients have metastatic RCC (mRCC) at first diagnosis, and 25% of patients with localized disease develop metastases after surgery.^[2]

Over the past few years, immunotherapy with interleukin (IL)-2 or interferon (IFN)- α was the established systemic therapy for patients with mRCC. However, the treatment strategy was denounced with poor efficacy and highly toxic effect.^[3] Therefore, except in certain circumstances, monotherapy with IFN- α or high-dose bolus IL-2 should no longer be routinely recommended as the first-line therapy in mRCC.

With advanced understanding of the molecular biology of RCC, there are various developed and approved drugs which inhibit vascular endothelial growth factor receptor signaling pathways (i.e., sorafenib, sunitinib, bevacizumab/IFN- α , pazopanib, and axitinib) or mammalian target of rapamycin pathways (i.e., temsirolimus and everolimus).^[4] Among the drugs, sunitinib and sorafenib were the most recommended choice for Category 1 and 2A patients with recurrent or medically unresectable dominant clear cell stage IV RCC (Network Kidney Cancer Panel [NCCN, Version 2.2017]).^[5]

Although a number of researches have compared efficacy and safety of sunitinib and sorafenib in RCC, there were always conflicted results. While the efficacy of sunitinib and sorafenib were well established, they are also associated with a number of potentially serious side effects including fatigue, hand-foot

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syndrome, rash, stomatitis, diarrhea, hypertension, and nausea that contribute to morbidity and mortality after treatment. The comparative efficacy and safety of sunitinib with sorafenib in the treatment of mRCC remains to be determined. It is hence necessary to find out the exact distinction between the 2 drugs. In this study, we performed a meta-analysis using published articles to systematically identify and summarize the efficacy and safety profiles of sunitinib vs sorafenib in patients with RCC.

2. Materials and methods

2.1. Relevant articles search strategy

A systematic search on PubMed/Medline, OVID/EMBASE, Cochrane Library, and ClinicalTrials.gov before February 28, 2018 was performed to find relevant studies. There were no language constraints. The keywords used for the literature search included sorafenib, sunitinib, RCC, and their variations or synonyms (see Supplemental Table S1, <http://links.lww.com/MD/D968>, which demonstrates the retrieval of the included study). Studies were included if they met the following criteria: they compared sunitinib with sorafenib; the patients were diagnosed with RCC. The primary outcomes of interest were progression-free survival (PFS), overall survival (OS), or adverse events (AEs).

2.2. Data extraction

The following information was extracted from all eligible studies: first author's name, published year, median age, percentage of male, trial phase, number of enrolled patients, median PFS (mPFS) (months), median OS (mOS) (months), and number of AEs. Other information extracted include the main study results such as hazard ratio (HR), 95% confidence interval (CI) for PFS and OS, number of cases with AEs, and information that did not belong to any previous mentioned categories but was related to the methodological quality of studies.

2.3. Assessment of methodological quality

The methodological quality of the included trials and the risk of bias were evaluated using the Cochrane Collaboration's tool for determining risk of bias. The domains implemented in the current systematic review concerned randomization and allocation concealment (selection bias), blinding (performance and detection bias), loss to follow-up, and keeping to the intention-to-treat principle (attrition bias), selective reporting (reporting bias), and other biases. We decided to put forth the meta-analysis of every study while offering a synopsis on the risk of bias across trials.

2.4. Data synthesis and statistical analysis

The HRs for PFS and OS with relative 95% CIs were extracted from each study. Risk ratio (RR) and corresponding 95% CIs were also calculated. Statistically significant heterogeneity was evaluated using the Cochran Q test and the degree of observed heterogeneity was evaluated by I^2 (ranging from 0%–100%). A Cochran's Q $P < .10$ was considered to show significant heterogeneity. The analysis was undertaken using the random effects model or otherwise, the fixed effects model. All the data were collected using Microsoft Office Excel 2007. Publication bias was investigated using funnel plots. Where information was missing, the researchers were contracted to seek the pertinent

information. Analyses were done in RevMan 5.3 (Cochrane Collaboration, 2014) and STATA14 (STATA Corp., College Station, TX). The study was documented based on the favor reporting items for systematic reviews and meta-analyses checklist. A P value $< .05$ suggested statistical significance for all analyses except for the tests of heterogeneity and between subgroup difference, for which the statistical significance level was set at $\alpha = 0.10$.

3. Results

3.1. Study selection and characteristics of included trials

We identified 2362 possibly relevant references (PubMed, 331; OVID/EMBASE, 1607; Cochrane Library, 420; and Clinical Trials, 4). After eliminating identical publications through titles and abstracts, 233 possibly qualified articles were identified. Finally, 14 studies were selected for full-text review based on preplanned inclusion criteria. Main reason of exclusion includes meta-analyses or review, duplicate publications, and studies evaluating nonclinical outcomes, efficacy, or safety. Finally, 6 studies were employed in this quantity analysis for adequate methodological quality and providing sufficient data (see Supplemental Figure S1, <http://links.lww.com/MD/D964>, which demonstrates the literature quantity analysis). There were 3112 patients contained in the meta-analysis, in which the effects of the administration of sunitinib (5 mg bid) were compared with those of the treatment with sorafenib (400 mg bid). Among these studies, 3 were performed on first-line, 2 on second-line, and 1 unclear. Full details of the selection process were disclosed in Figure 1 and the main characteristics of included studies were displayed (see Supplemental Table S2, <http://links.lww.com/MD/D969>, which demonstrates the main characteristics of the included study).

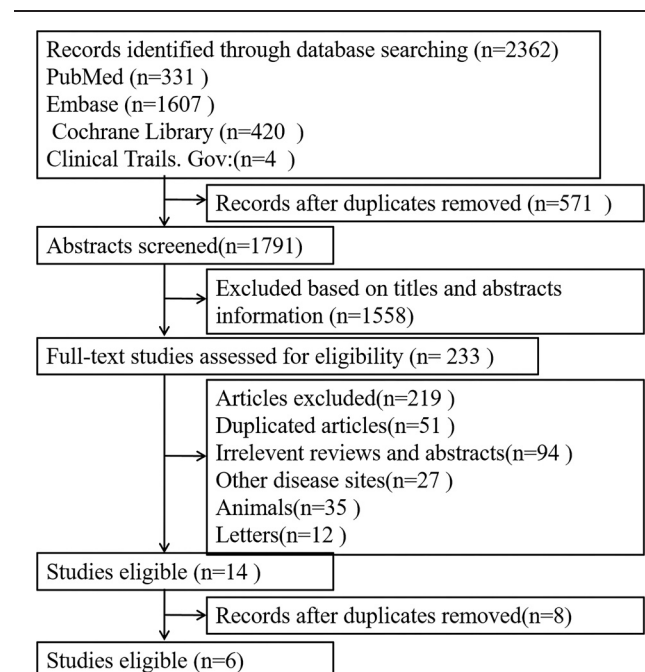


Figure 1. Flow chart.

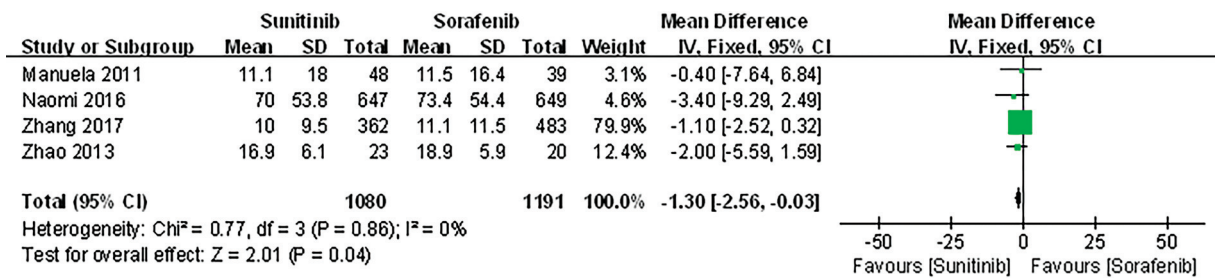


Figure 2. The mPFS in overall population treatment with sunitinib over sorafenib. CI = confidence intervals, mPFS = median progression-free survival.

3.2. Efficacy of sorafenib and sunitinib in RCC

The data for mPFS was available from 4 studies for a total of 2271 patients. Among these, 1191 received sorafenib and 1080 received sunitinib. The cumulative data showed that sorafenib group exhibited higher mPFS compared to sunitinib group (mean difference, -1.3; 95% CI, -2.56 to -0.03; I², 0%; P=.04; Fig. 2), substantial heterogeneity was observed in the meta-analyses for PFS. However, mOS was similar in sorafenib and sunitinib group (MD, -0.48; 95% CI, -3.40-2.43; I², 0%; P=.74; Fig. 3), no heterogeneity was observed in the meta-analyses for OS.

When the analysis was limited to patients treated with first or second-line therapy, a significant benefit in terms of prolonging the mPFS was found for sorafenib compared to sunitinib in first-line treatment (MD, -1.33; 95% CI, -2.61 to -0.04; I², 0%; P=.04), but not in second-line treatment (MD, -0.4; 95% CI, -7.64-6.84), and there was no significant heterogeneity for both first and second-line therapy. When the analysis was limited to patients from Asian or the United States and Europe, no significant benefit in terms of mPFS was found for sorafenib

compared to sunitinib (MD, -1.22; 95% CI, -2.54-0.10; I², 0%; P=.07), (MD, -2.21; 95% CI, -6.77-2.36; I², 0%; P=.34), and there was no significant heterogeneity.

Meta-analyses of 2 studies with relevant data^[6,7] showed that sunitinib significantly reduced the risk of PFS compared to sorafenib (HR, 0.71; 95% CI, 0.6-0.82, P=.55; Fig. 4). Sunitinib also significantly reduced the risk of OS compared to sorafenib (HR, 0.79; 95% CI, 0.65-0.92, P=.55; Fig. 5), no heterogeneity was observed in the meta-analyses for PFS and OS.

3.3. Safety of sorafenib and sunitinib in RCC

Three trials^[7-9] involving 1332 patients were conducted to assess AEs of all grades. The main AEs involved in rash, fatigue, hand-foot syndrome, nausea, stomatitis, diarrhea, hypertension, hypothyroidism, decreased appetite, dehydration, pruritus, vomiting, pain, taste disturbance, and neutropenia. There were no differences in the incidence of fatigue, hand-foot syndrome, pruritus, nausea, taste disturbance, stomatitis, diarrhea, hypertension, hypothyroidism, neutropenia, vomiting, and pain (Fig. 6 and see Supplemental Table S3, <http://links.lww.com/MD/D970>,

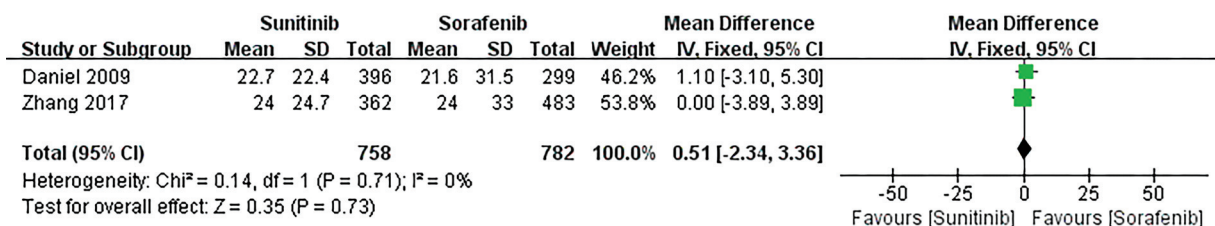


Figure 3. The mOS in overall population treatment with sunitinib over sorafenib. CI = confidence intervals, mOS = median overall survival.

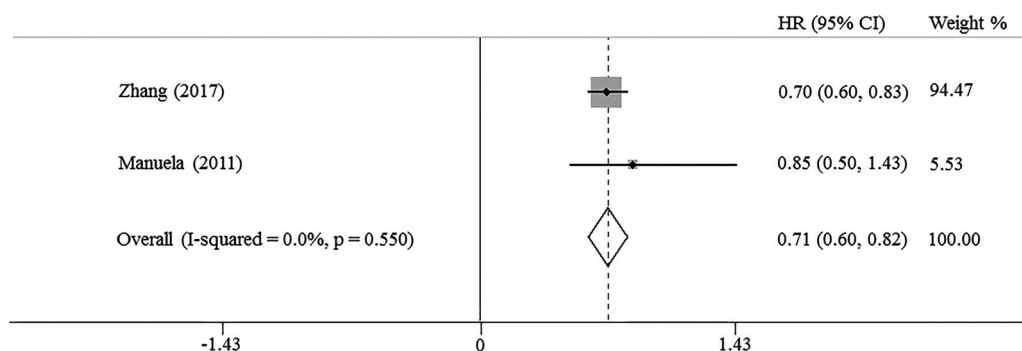


Figure 4. HR for PFS in overall population treatment with sunitinib over sorafenib. CI = confidence intervals, HR = hazard ratio, PFS = progression-free survival.

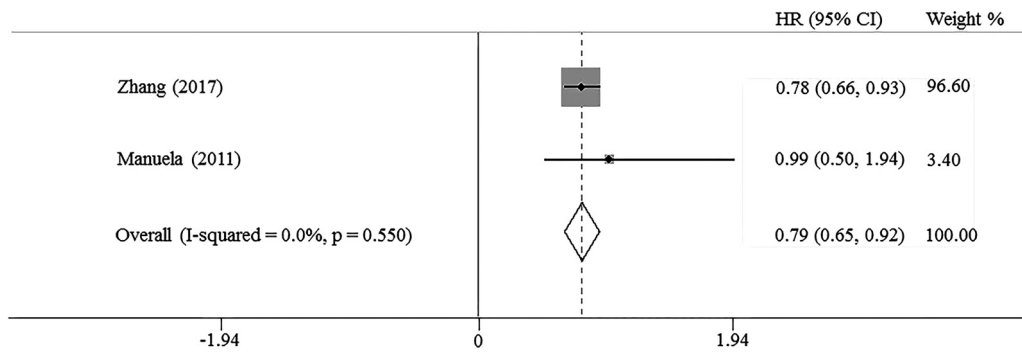


Figure 5. HR for OS in overall population treatment with sunitinib over sorafenib. CI = confidence intervals, HR = hazard ratio, OS = overall survival.

which demonstrates the AEs of sunitinib vs sorafenib). However, the risk of rash (RR, 0.31; 95% CI, 0.12–0.79) was greater in sunitinib group than that in sorafenib group, while the risk of decreased appetite (RR, 2.10; 95% CI, 1.33–3.30) and dehydration (RR, 2.73; 95% CI, 1.14–6.56) were smaller in contrast (see Supplemental Figures S2–S4, <http://links.lww.com/MD/D965>, <http://links.lww.com/MD/D966>, <http://links.lww.com/MD/D967>, which demonstrates the risk of rash, appetite, and dehydration between the 2 groups).

4. Discussion

In recent years, targeted therapies have changed the treatment landscape of RCC. Tyrosine kinase would become the most

common treatment of RCC, especially sorafenib and sunitinib. We firstly investigated the therapeutic effectiveness of sorafenib and sunitinib in RCC. Sunitinib was found to have a clinical advantage over sorafenib. However, side effect profiles of the targeted agents, such as hypothyroidism, hypertension, rash, hand-foot syndrome, and fatigue should be critically considered in clinical treatment choices.^[10,11]

Sorafenib and sunitinib were approved more than a decade ago and since were widely used for terminal RCC by Food and Drug Administration. Since then a large amount of clinical studies had tried to elucidate the efficacy and safety of the novel treatments. Compared with standard chemotherapy, epidermal growth factor receptor-tyrosine kinase inhibit were effective in improving PFS and OS of patients with RCC.^[12,13] Filson et al^[14] reported

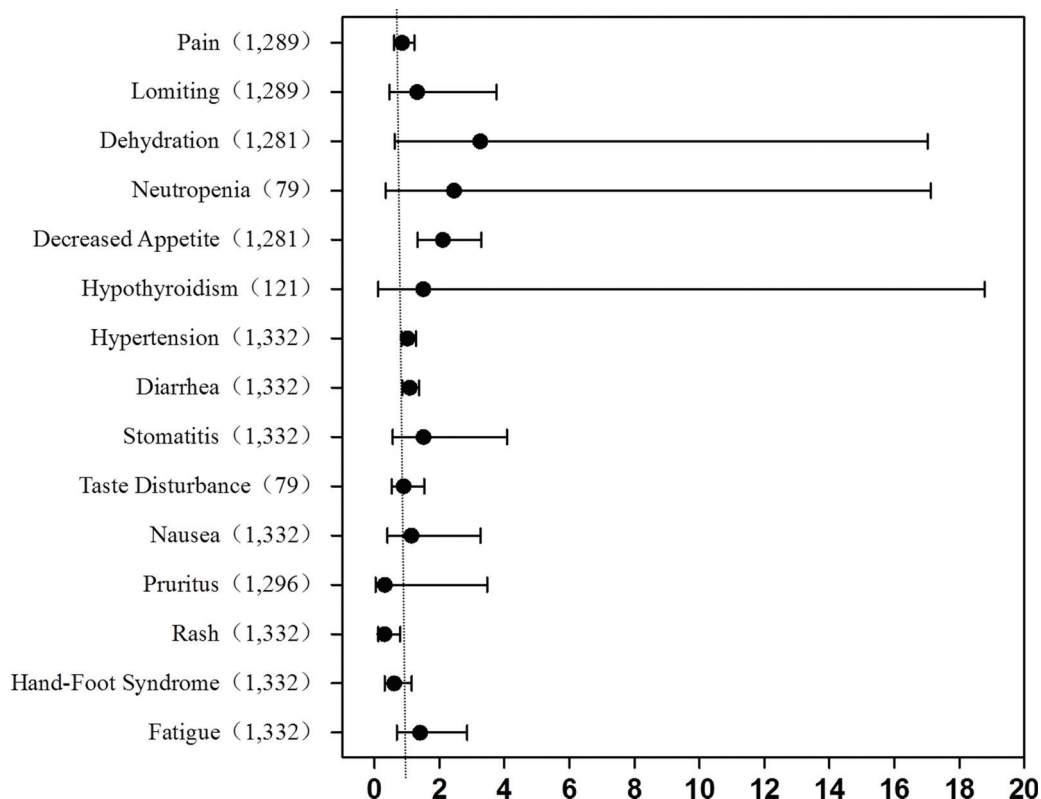


Figure 6. Pooled risk ratio estimates and 95% confidence intervals for adverse events.

that patients in first-line treatment with sorafenib had high probability of proceeding to second-line treatment with sunitinib, indicating the difference between efficacies of the 2 drugs. In our research, we performed a comprehensive analysis of all available randomized studies involving sorafenib and sunitinib for the treatment of RCC. We reported that sorafenib was more active in prolonging the average PFS than sunitinib, substantial heterogeneity was observed in the meta-analyses for PFS. Specifically, sorafenib could obviously prolong mPFS (MD, -1.3 ; 95% CI, -2.56 to -0.03), but not OS, compared to sunitinib. Interestingly, our meta-analysis found that the administration of sunitinib was associated with a significant benefit over sorafenib treatment in terms of reducing the risk of PFS (HR, 0.71; 95% CI, 0.6–0.82,) and OS (HR, 0.79; 95% CI, 0.65–0.92).

Although our findings indicated that sorafenib application had a certain survival benefit in prolonging mPFS when compared to that of sunitinib. We also applied HR to verify the relative efficacy of sorafenib and sunitinib therapy in patient with RCC. HR served as a time-independent indicator to evaluate the RR of intervention group vs normal group. HR was much better than any other indicator to response the realistic results.^[15] Our analysis showed that sunitinib significantly reduced the risk of PFS and OS compared to sorafenib. Sorafenib, however, could provide patients with a little higher mPFS. Generally speaking, there are contradictions in terms of mPFS and HR of PFS, which is why it is difficult to draw a definite conclusion on drug efficacy based on current evidence. It was worth noting that there were only 4 and 2 research literatures providing mPFS and HR of PFS, respectively. Among the 2 research literatures providing of HR, patients classified under Memorial Sloan Kettering Cancer Center (MSKCC) moderate risk were treated with sorafenib, whereas patients classified under MSKCC high risk were treated with sunitinib. Interesting, Manuela^[6] observed that the mPFS of euthyroid patients who received sorafenib patients was consistent with previous reports (5.5 months), whereas hypothyroid patients who received sorafenib achieved a mPFS of 19 months. And sunitinib might be more effective in patients classified under MSKCC high risk. In fact, the variation in race, age, first or second therapy might also contribute to the difference in results. Therefore, more studies were required for us to illuminate the absolute or relative predominance between sunitinib and sorafenib on PFS or OS.

The comparative efficacy and safety of sunitinib with sorafenib in the treatment of RCC remains to be determined. Early evidence-based studies suggested the greater efficacy of sorafenib over other chemotherapy drugs both first and second-line treatment.^[16] Unfortunately, the spatial studies found that Tinib presented the greater negative first-line data over IFN combined other drugs, which excluded its routine use in this setting, and TAs was now limited to treating certain categories of patients in the treatment of mRCC.^[17] Until now, many studies have focused on comparative efficacy and safety of TAs and other chemotherapy drugs, but few studies are focused on the comparative efficacy and safety between TAs, such as sunitinib and sorafenib in the treatment of RCC. Zhang et al^[7] found similar effectiveness on PFS and OS of sorafenib and sunitinib in treating Chinese patients with mRCC. However, sorafenib was found to be more effective for elderly patients than sunitinib. Iacovelli et al,^[15] however, found TAs to be marginally better, but not significant, in first-line treatment and no difference in second-line treatment. Our study found the benefit of prolonging mPFS for sorafenib as

compared to sunitinib, with a significant difference between the 2 TAs in first-line treatment and no difference in second-line treatment, inconsistent with Iacovelli et al's result.^[15] Based on this, different patients with different prognostic characteristics must be considered in trials when the analysis was limited to patients received first or second-line therapy,^[15] because recent analyses reported as the outcome of patients both first and second-line of therapy might be different based on the prognostic class.

A subanalysis of Asian patients in a phase 3 trial revealed a significant mPFS advantage of sorafenib treatment over sunitinib, replicating past Chinese, Korean, and Italian researches which found similar results.^[4] In contrast, comprehensive studies on the clinical outcomes found sunitinib to manifest more consistent efficacy and safety outcomes than sorafenib, accompanied with significantly more common adverse effects for elder population.^[7] In our research, we found greater effects of prolonged mPFS using sorafenib compared to sunitinib in Asian population, although the benefit remains small and nonsignificant. There was no difference between sorafenib and sunitinib on mPFS in the United States and Europe. In line with our findings, a Swedish register-based demonstrated no difference between sorafenib and sunitinib in the duration of treatment or time to death.^[18] The discrepancy might be related to diversity of patient populations enrolled in each study differing in many aspects related to prognosis and ethnicity. Furthermore, this suggested that patients with different prognostic profiles needed different approaches. All the included studies were conducted in selected patients with adequate organ function and no severe comorbidities at the time of study entry. It was well known that clinical trial data might not always reflect the activity in an unselected patient population in clinical practice.^[19]

Drug tolerability could influence clinical decision and should be considered in guiding therapy, as studies have reported a large number of patients with RCC were lost with subsequent therapy. In our study, there were no marked differences in most AEs between the 2 drugs. However, the risk of rash was greater in patients exposed to sunitinib compared to sorafenib, while decreased appetite and dehydration were smaller in contrast. Hence, according to Adverse drug reaction occurrence of patients, it is best to offer specialized chemotherapy for different individuals. Patients with liver dysfunction, for example, should be prescribed sorafenib as there were sunitinib users reporting severe hepatotoxicity. In addition, occurrence of AEs like diarrhea, hypertension, and taste disturbance tend to be higher in sunitinib usage compared to sorafenib, although the difference is not statistically significant, while hand–foot–mouth syndrome occurring was significantly higher in sorafenib usage. These results reminded us of more choice when patients were faced with more related basic diseases. Moreover, Buchler et al^[20] reported that when sorafenib and sunitinib were used as the second therapy, the overall adverse serious events were statistically lower ($P = .031$ for sunitinib and $P < .001$ for sorafenib). The rate of serious AEs was significantly lower for sorafenib–sunitinib than sunitinib–sorafenib ($P < .001$). This indicates a probable cross-tolerance and adaptation between sorafenib and sunitinib. A major limitation of this research was that the number of studies available for comparing sorafenib and sunitinib was very limited. This prevented us from drawing a firm conclusion about their comparative effects in some settings. Therefore, the results for risk elements require future studies with larger sample populations.

5. Conclusion

Here, the current analysis shows that as compared with sorafenib, sunitinib may provide patients with certain benefits to reduce the risk of PFS and OS, especially for the patients classified under MSKCC high risk. However, a certain significant difference with sunitinib and sorafenib was found in terms of prolonging the average PFS when sorafenib was used as first-line treatment in Asian patient classified under MSKCC moderate risk. The analysis of AEs revealed that the risk of rash was greater in patients converted to sunitinib than in patients remaining on sorafenib, while decreased appetite was smaller in contrast. Sorafenib remained a nondetrimental option for therapy of RCC, especially for patients with liver dysfunction or difficulty in feeding, whether in first or second-line treatment. And, compared with sorafenib, sunitinib reduced the risk of PFS and OS, even if sunitinib was a better treatment option for RCC treatment for patients faced with severe skin reaction.

In short, sunitinib was a better treatment option for RCC treatment while patients faced with severe skin reaction. And for those Asian patients classified under MSKCC moderate risk, whether in first or second-line treatment, had difficulty in feeding, sorafenib is a better choice for prolong mPFS.

Author contributions

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