Medical Oncology (2019) 36:6
https://doi.org/10.1007/s12032-018-1231-3

ORIGINAL PAPER

# Comparison of axitinib and sunitinib as first-line therapies for metastatic renal cell carcinoma: a real-world multicenter analysis

Sakae Konishi[1] · Shingo Hatakeyama[1] · Toshiaki Tanaka[2] · Yoshinori Ikehata[3] · Toshikazu Tanaka[1] · Naoki Fujita[1] · Yusuke Ishibashi[1] · Hayato Yamamoto[1] · Takahiro Yoneyama[1] · Yasuhiro Hashimoto[1] · Kazuaki Yoshikawa[4] · Toshiaki Kawaguchi[5] · Naoya Masumori[2] · Hiroshi Kitamura[3] · Chikara Ohyama[1]

Received: 19 October 2018 / Accepted: 21 November 2018 / Published online: 24 November 2018


## Abstract

We aimed to compare oncological outcomes and safety of axitinib and sunitinib in patients with treatment-naïve metastatic renal cell carcinoma (mRCC). We retrospectively evaluated 169 patients with mRCC who were treated with axitinib or sunitinib as the first-line therapy in five hospitals between October 2008 and August 2018. Oncological outcomes and safety were compared between axitinib ($n=68$) and sunitinib ($n=101$) groups. Inverse probability of treatment weighted (IPTW)-adjusted Cox regression analysis was performed to evaluate effects of first-line therapies on progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS). Patients in the axitinib group were significantly older (66 vs. 72 years) than those in the sunitinib group. Median relative dose intensity was significantly higher in the axitinib group ($94 \pm 62\%$) than in the sunitinib group ($65 \pm 20\%$; $P=0.001$). Objective response rate was significantly higher in the axitinib group (21%) than in the sunitinib group (10%; $P=0.042$). IPTW-adjusted Cox regression analysis revealed significant differences in CSS and OS but not in PFS between the two groups. Safety in terms of grade $\geq 3$ adverse events was significantly different between the axitinib (34%) and sunitinib (55%) groups ($P=0.006$). Compared with sunitinib, axitinib significantly prolonged CSS and OS and showed a safer profile as the first-line therapy for treatment-naïve mRCC.

**Keywords** Axitinib · Sunitinib · Metastatic renal cell carcinoma · First-line therapy · Safety · Efficacy

## Abbreviations

| | |
|---|---|
| mRCC | Metastatic renal cell carcinoma |
| TKIs | Tyrosine kinase inhibitors |
| VEGF | Vascular endothelial growth factor |
| ECOG PS | Eastern Cooperative Oncology Group performance status |
| IMDC | International Metastatic Renal Cell Carcinoma Database Consortium |
| CR | Complete response |
| PR | Partial response |
| SD | Stable disease |
| PD | Progressive disease |
| PFS | Progression-free survival |
| CSS | Cancer-specific survival |
| OS | Overall survival |
| IPTW | Inverse probability of treatment weighted |
| HR | Hazard ratio |
| 95% CI | 95% confidence interval |
| IQR | Interquartile range |
| RDI | Relative dose intensity |
| mTORi | Mammalian target of rapamycin inhibitor |

## Introduction

Survival rates of patients with metastatic renal cell carcinoma (mRCC) have remarkably improved since the introduction of tyrosine kinase inhibitors (TKIs) [1–3]. Currently available TKIs included sunitinib, pazopanib, axitinib, and sorafenib. Sunitinib is widely prescribed as the first-line therapy for mRCC [4, 5]; however, severe toxicities have resulted in up to 50% dose reduction, interruption, and/or schedule alternation of sunitinib, leading to a low relative dose intensity [6–11]. Axitinib—a potent, selective inhibitor of vascular endothelial growth factor receptors 1–3 is approved as the second-line therapy for mRCC [12]. Although axitinib has failed to demonstrate improved efficacy over sorafenib in the first-line setting, previous studies

✉ Shingo Hatakeyama
shingoh@hirosaki-u.ac.jp

Extended author information available on the last page of the article

have anticipated its clinical activity with a higher response rate and more acceptable safety profile as the first-line therapy for mRCC compared with sorafenib's clinical activity [1, 2]. In addition, axitinib might show the same efficacy as sunitinib as the first-line therapy in patients with mRCC since no significant difference was detected in efficacy and safety of sorafenib and sunitinib as first-line therapies [13, 14]. However, no previous study has compared the efficacy and safety of first-line axitinib and sunitinib. Thus, in this study, we retrospectively compared the safety and oncological outcomes of axitinib and sunitinib as first-line therapies for treatment-naïve mRCC in the real-world setting.

## Materials and methods

### Design and ethics statement

The present retrospective, multicenter study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the Ethics Committee of Hirosaki University School of Medicine (authorization number, 2017-089). Pursuant to the provisions of the ethics committee and the ethics guideline in Japan, written consent was not required in exchange for public disclosure of study information (opt-out approach) in the case of retrospective and/or observational study using a material such as the existing documentation.

### Patient selection and demographics

From October 2008 to August 2018, 169 patients with mRCC were treated with axitinib or sunitinib as the first-line therapy in five tertiary institutions. Analyzed variables included age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), clinical stage, metastatic sites and numbers, and history of radical nephrectomy. Tumor stage and grade were stratified in accordance with the 2009 TNM classification of the Union of International Cancer Control. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model was applied for risk stratification [15]. Targeted therapy treatments at the recommended dosage (sunitinib 50 mg orally daily, 4 weeks on and 2 weeks off or axitinib 10 mg orally daily) were continued until disease progression, an adverse event depending on its type and severity, or the physician's discretion. The patients were followed every 2–4 weeks thereafter during the administration of any targeted therapy. A computed tomography was generally performed every 3–4 months. Additional radiological investigations were performed when clinically indicated.

### Outcomes

Tumor response was analyzed using Response Evaluation Criteria in Solid Tumors version 1.1, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Oncological outcomes were compared between axitinib and sunitinib groups, including progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS). A first-line TKI failure-free survival rate was estimated from initial TKI therapy to initial PD or toxicity-related discontinuation of TKI. The grade of adverse events was evaluated by the Common Terminology Criteria for Adverse Events version 4.0.

### Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (SPSS, Inc., Chicago, IL), GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), and R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Fisher's exact test or $\chi^2$ test. Quantitative variables were expressed as mean with standard deviation or median with interquartile range (IQR). Intergroup difference was tested by Student's *t*-test or the Mann–Whitney *U*-test. PFS, CSS, and OS from initial TKI treatment until disease progression in PFS, cancer death in CSS, and any death in OS were estimated using the Kaplan–Meier curve and the log-rank test. The inverse probability of treatment weighted (IPTW)-adjusted Cox regression analysis was performed to evaluate the impact of first-line therapies on PFS, CSS, and OS. The IPTW model reweighs affected and unaffected groups to mimic a propensity score-matched population [16–23]. Hazard ratios (HRs) with 95% confidence interval (95% CI) were calculated after controlling for potential confounders, including patient demographics and clinicopathological tumor variables. Variables included in the IPTW analysis were age, sex, ECOG PS, IMDC risk score, metastatic disease at diagnosis, history of radical nephrectomy, and non-clear histology.

## Results

### Baseline characteristics

The number of patients in the axitinib and sunitinib groups was 68 and 101, respectively. Median patient age was 68 years; patients in the axitinib group were significantly older (median age; 66 vs. 72 years; $P < 0.001$) than those in the sunitinib group (Table 1). In addition, there were significant difference between the axitinib and sunitinib groups

**Table 1** Background of patients

| *n* | Axitinib 68 | Sunitinib 101 | *P* value |
|---|---|---|---|
| Age, years (±SD) | 69.9 ± 10.7 | 63.6 ± 10.8 | < 0.001 |
| Male | 50 (74%) | 77 (76%) | 0.719 |
| ECOG PS > 1 | 10 (15%) | 2 (2.0%) | 0.004 |
| TNM | | | 0.006 |
| cT1-2 | 20 (29%) | 53 (53%) | |
| cT3-4 | 46 (68%) | 44 (44%) | |
| cTx | 2 (2.9%) | 4 (4%) | |
| cN+ | 12 (18%) | 33 (33%) | 0.030 |
| Metastatic disease at diagnosis | 51 (75%) | 57 (56%) | 0.014 |
| History of nephrectomy | 30 (44%) | 71 (70%) | 0.001 |
| IMDC risk model | | | 0.221 |
| Favorable | 5 (7.4%) | 17 (16%) | |
| Intermediate | 32 (47%) | 45 (44%) | |
| Poor | 28 (41%) | 36 (36%) | |
| Unknown | 3 (4.4%) | 3 (3.0%) | |
| Sites of mets (in total) | | | |
| Visceral mets | 52 | 83 | |
| Lymph node | 14 | 38 | |
| Bone | 9 | 34 | |
| Others | 18 | 20 | |
| Number of metastatic organs | 1.4 ± 0.9 | 1.7 ± 0.9 | 0.059 |
| Histology | | | 0.632 |
| Clear | 65 (96%) | 79 (78%) | |
| Clear with spindle | 3 (4.4%) | 4 (4.0%) | |
| Non-clear | 3 (4.4%) | 7 (6.9%) | |
| Unknown | 0 | 11 (11%) | |
| Median follow-up (months) | 18 (9.6–32) | 17 (8.3–35) | 0.677 |
| Deceased | 30 (44%) | 60 (59%) | 0.051 |

in term of the number of patients with ECOG > 1 (15% vs. 2.0%; $P = 0.004$), cT stage ($P = 0.006$), and presence of metastatic disease at diagnosis (75% vs. 56%; $P = 0.014$). Median initial dosage of the first-line therapy in the axitinib and sunitinib groups was 10 mg (IQR 10–10) and 50 mg (IQR 37.5–50 mg), respectively. Alternative scheduling was used in 13% of the patients in the sunitinib group. The number of patients with nephrectomy was significantly lower in the axitinib group (44%) than in the sunitinib group (70%; $P = 0.001$). Median follow-up period (18 vs. 17 months) and IMDC risk stratification (Fig. 1A) were not different between the two groups. Metastatic sites were significantly different in between the groups (lymph node; $P = 0.017$, and bone; $P = 0.004$; Fig. 1B). The second-line regimens were not significantly different between the groups [axitinib group: TKI, 50%; mammalian target of rapamycin inhibitor (mTORi), 30%; nivolumab, 20%; and interferon, 0%; sunitinib group: TKI, 51%; mTORi, 30%; nivolumab, 12%; and interferon, 7.4%] ($P = 0.395$).

## Oncological outcomes

Median relative dose intensity (RDI) was significantly higher in axitinib group (94 ± 62%) than in the sunitinib group (65 ± 20%) (Fig. 2a, $P = 0.001$). Significantly higher rate of toxicity-related discontinuation was observed in the sunitinib group (39%) than in the axitinib group (22%) (Fig. 2b, $P = 0.023$). Objective response rate was significantly higher in the axitinib group (21%) than in the sunitinib group (10%) (Fig. 2c, $P = 0.042$). There were no significant differences in PFS (Fig. 2d), CSS (Fig. 2e), and OS (Fig. 2f) between the axitinib and sunitinib groups before the background adjustment. However, IPTW-adjusted Cox regression

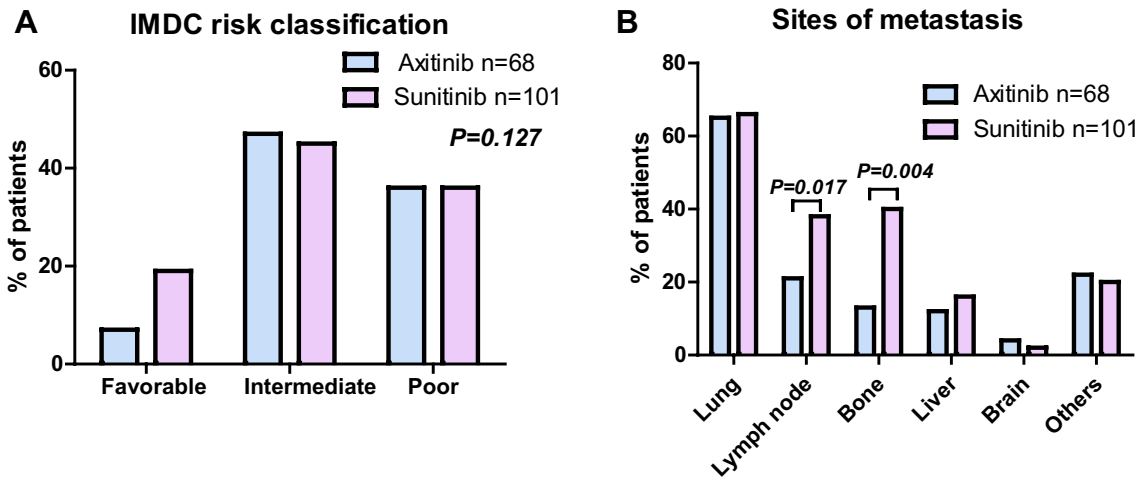


**Fig. 1** There was no significant difference in IMDC risk stratification between the axitinib and sunitinib groups (**a**, $P = 0.127$). Metastatic sites were significantly different between the axitinib and sunitinib groups in lymph node (21% and 38%, respectively, $P = 0.034$) and bone (13% vs. 40%, respectively, $P < 0.001$) (**b**)

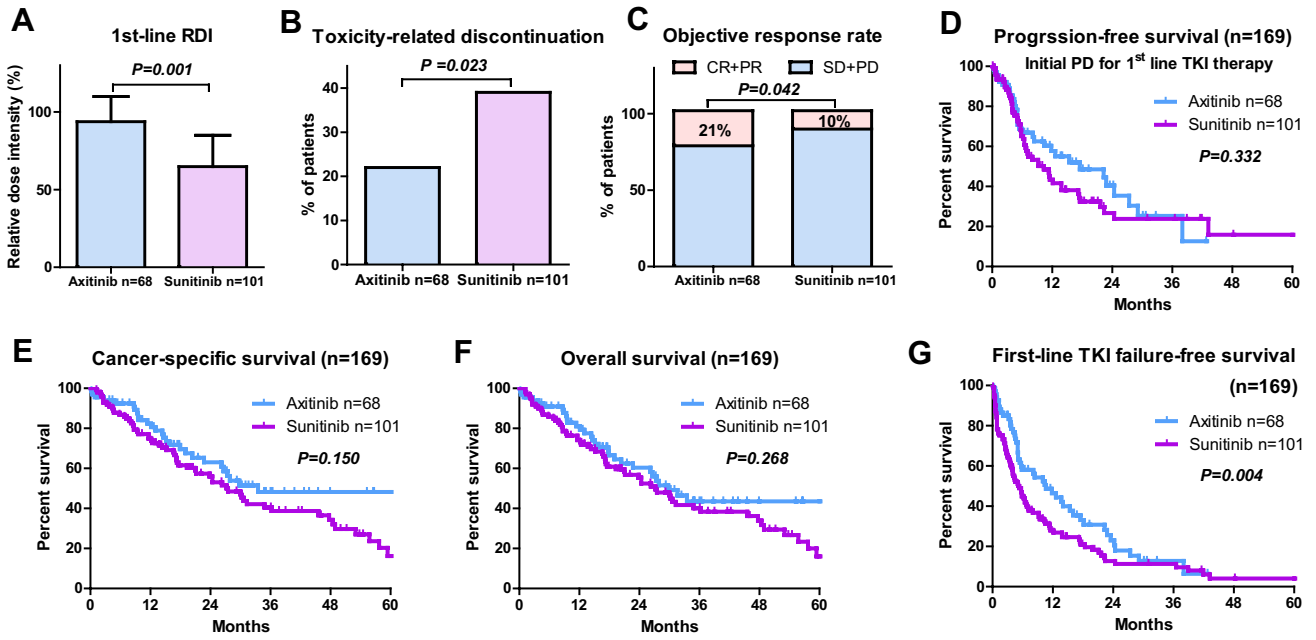


**Fig. 2** Median relative dose intensity (RDI) was significantly higher in axitinib group (94 ± 62%) than in the sunitinib group (65 ± 20%) (**a**, $P = 0.001$). Significantly higher rate of toxicity-related discontinuation was observed in the sunitinib group (39%) than in the axitinib group (22%) (**b**, $P = 0.023$). Objective response (CR + PR) rate was significantly higher in the axitinib group (21%) than in the sunitinib group (10%) (**c**, $P = 0.042$). Before the background adjustment, there were no significant differences in PFS (**d**), CSS (**e**), and OS (**f**) between the axitinib and sunitinib groups. The first-line TKI failure-free survival was significantly longer in the axitinib group than that in the sunitinib group (**g**, $P = 0.004$)

**Table 2** IPTW-adjusted Cox regression analysis for prognosis

| IPTW-adjusted model | Factor | *P* value | HR | 95%CI |
|---|---|---|---|---|
| Progression-free survival | First-line axitinib | 0.251 | 0.74 | 0.44–1.24 |
| Cancer-specific survival | First-line axitinib | 0.002 | 0.37 | 0.19–0.69 |
| Overall survival | First-line axitinib | 0.003 | 0.39 | 0.21–0.72 |

analyses revealed significant differences in CSS (HR 0.37, $P = 0.002$) and OS (HR 0.39, $P = 0.003$) but not in PFS (HR 0.74, $P = 0.251$) between the two groups (Table 2). The first-line TKI failure-free survival was significantly longer in the axitinib group than that in the sunitinib group (Fig. 2g). The PD rate for the second-line therapy was significantly different between the first-line axitinib and sunitinib groups (26% and 52%, respectively, $P = 0.019$), although there was no significant difference in the second-line regimens between the groups. Regarding safety, significantly higher rate of grade ≥ 3 toxicity was observed in the sunitinib group (55%) than in the axitinib group (34%; $P = 0.006$; Fig. 3a). The rate of grade ≥ 3 hypertension was significantly higher in the axitinib group (18%) than in the sunitinib group (6.9%; $P = 0.031$; Fig. 3b), whereas that of hematological toxicities were significantly higher in the sunitinib group (34%) than in the axitinib group (7.4%; $P < 0.001$; Fig. 3b). In patients aged ≥ 70 years, significantly higher rates of grade ≥ 3 toxicities were observed in the sunitinib group than in the axitinib group ($P < 0.001$; Fig. 4a); rates of grade ≥ 3 acute kidney injuries (22% vs. 2.4%, respectively; $P = 0.013$; Fig. 4b) and hematological toxicities (41% vs. 5.0%, respectively; $P < 0.001$; Fig. 4b) were significantly higher in the sunitinib group than in the axitinib group.

## Discussion

In this study, we for the first time compared oncological outcomes and safety of first-line axitinib and sunitinib in patients with treatment-naïve mRCC. A few studies have investigated the efficacy and safety of axitinib as the first-line therapy for mRCC [1, 2, 15, 24–28]. IPTW-adjusted multivariate analyses revealed that CSS and OS were significantly prolonged in the axitinib group than in the sunitinib group. However, these outcomes were contradictory to those reported in a previous randomized phase III trial [1]. In a previous study, there was no significant difference in OS between axitinib and sorafenib in the first-line therapy of mRCC [2] although potential benefits for PFS were observed in axitinib [1] in patients with a median age of 58 years. The potential reason for significantly improved outcomes

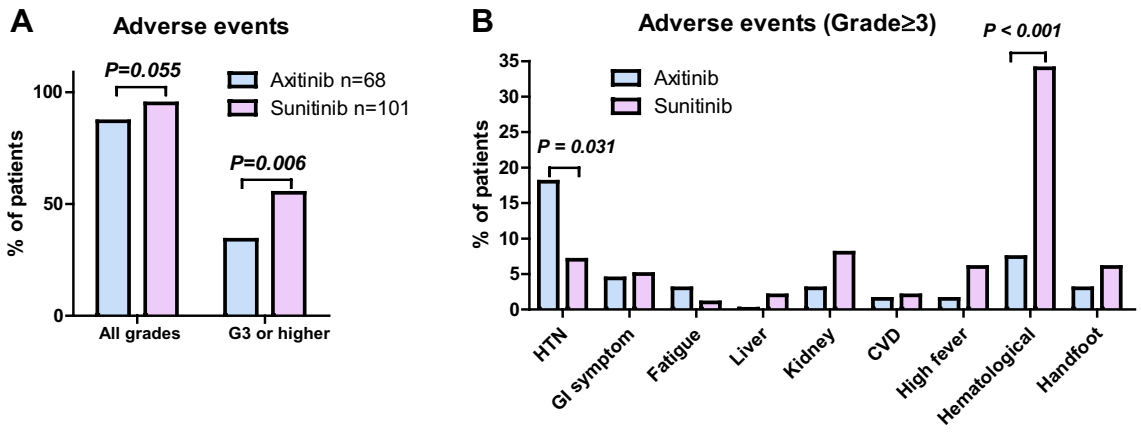


**Fig. 3** Significantly higher rate of grade ≥ 3 toxicity was observed in the sunitinib (55%) groups than in the axitinib group (34%) (**a**, $P = 0.006$). The rate of grade ≥ 3 hypertension was significantly higher in the axitinib group (18%) than in the sunitinib group (6.9%) ($P = 0.031$), whereas that of hematological toxicities was significantly higher in the sunitinib group (34%) than in the axitinib group (7.4%) ($P = 0.001$) (**b**)

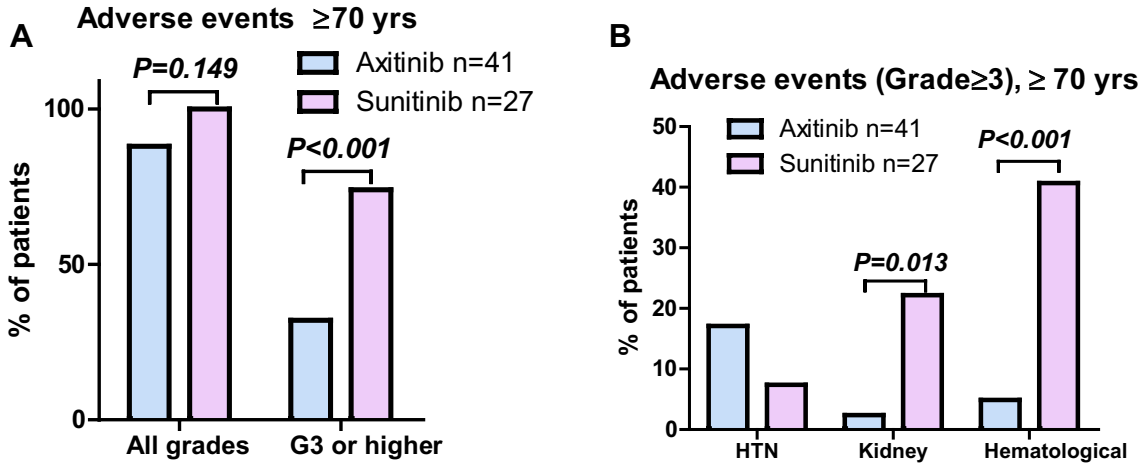


**Fig. 4** In patients aged ≥ 70 years, significantly higher rate of grade ≥ 3 toxicities was observed in the sunitinib group than in the axitinib group (**a**, $P < 0.001$). Rates of grade ≥ 3 acute kidney injury (7.9% vs. 2.9%, respectively; $P = 0.013$) and hematological toxicities (41% vs. 5.0%, respectively; $P < 0.001$) were significantly higher in the sunitinib group than in the axitinib group (**b**)

in the present study might be significantly higher RDI and objective response rate in the axitinib group than in the sunitinib group in the real-world elderly population. Oncological outcomes could be different between the previous phase III trials and the present study owing to a difference of 10 years in median patient age (58 vs. 68 years). In addition, significantly higher rate of toxicity-related discontinuation was observed in the sunitinib group than in the axitinib group. The long-term effect of sunitinib-related toxicities is an important factor for poor prognosis [10]. Although there was no significant difference in the PFS between the groups, the first-line TKI failure-free survival was significantly longer in the axitinib group, suggesting that full-dose and less toxic therapy for elderly patients might have contributed to prolong the prognosis in this study. Moreover, the effect of the second-line therapy should be noted. The PD rate for the second-line therapy was significantly higher in the first-line sunitinib group (52%) than that of first-line axitinib group (26%) in the present study, although there was no significant difference in the second-line regimens between the groups. These results may suggest that initial adequate therapy is important for better oncological outcomes and that it induces drug resistance. Despite the disadvantages of age and high prevalence of non-nephrectomy population in the axitinib group in this study, significantly prolonged CSS and OS suggested potential benefits of the first-line axitinib therapy for elderly patients with treatment-naïve mRCC.

The essential finding in this study is the adverse event profiles of the drugs. The most frequently reported grade ≥ 3 adverse events are hypertension with axitinib [1] and hypertension, neutropenia, and thrombocytopenia with sunitinib [29]. Sunitinib is reportedly associated with a significant side effect burden, with 19% of patients the discontinuing sunitinib due to adverse events and 50% requiring a dose reduction [10]. In the present study, we found significantly higher rates of grade ≥ 3 adverse events in the sunitinib group (55%) than that in the axitinib group (34%). Rates of grade ≥ 3 hematological events were significantly higher in the sunitinib group than in the axitinib group (34% vs. 7.4%, respectively), whereas rate of hypertension was significantly higher in the axitinib group than in the sunitinib group (18% vs. 7.0%, respectively). In elderly (≥ 70 years) patients, significantly higher rates of grade ≥ 3 adverse events were observed in the sunitinib group than that in the axitinib group (74% vs. 32%, respectively). In addition, the difference in grade ≥ 3 hematological events was extended in the sunitinib group than in the axitinib group (41% vs. 5.0%, respectively) in the elderly. Moreover, kidney-related adverse events were significantly higher in the sunitinib group than in the axitinib group (22% vs. 2.4%, respectively). Unfortunately, adverse event profiling based on retrospective analysis might be inaccurate and inadequate to address the difference in safety profile. However, record omission of grade ≥ 3 hematological events and hypertension is not frequent in the general practice. Therefore, our observation is relatively certain in terms of these two events. Although we could not address the major adverse events for the discontinuation of first-line therapy, higher rate of severe toxicity prevents enough dosing of sunitinib in the elderly patients, which may in turn lead to significant difference in oncological outcomes.

Several limitations of the present study must be acknowledged. First, we were unable to control for selection bias and other unmeasurable confounders due to the retrospective study design. It prevented us from reaching definitive conclusions regarding the effect of first-line TKIs on oncological outcomes. Second, the accuracy of adverse event profiling based on retrospective analysis might be not enough. Third, there may be a regional bias, and our results may not be generalizable in other populations owing to differences in medical practices. Nonetheless, to the best of our knowledge, this study represents the first comparative account of oncological outcomes and safety of axitinib and sunitinib as first-line therapies in real-world patients with treatment-naïve mRCC using IPTW-adjusted analysis. Although we could not come to a definitive conclusion regarding difference in efficacy between the two TKIs, clinical trials comparing a combination of immune checkpoint inhibitors plus axitinib (study arm) with sunitinib (control arm) may elucidate the global trend for selecting favorable TKIs for mRCC [30]. Notably, sunitinib—the standard first-line therapy for mRCC—was not selected in previous study arms due to intolerability [7–9]. Further research is warranted to address clinical benefit of first-line axitinib in patients with mRCC.

## Conclusion

Axitinib may significantly prolong CSS and OS compared with sunitinib, and showed a safe toxicity profile in patients with treatment-naïve mRCC, especially in elderly patients.

**Acknowledgements** The authors would like to thank Takuma Narita, Teppei Okamoto, Itsuto Hamano, Hirotaka Horiguchi, Masaaki Oikawa, Daisuke Noro, Kazuhisa Hagiwara, Yuki Fujita, Yukie Nishizawa, and Satomi Sakamoto for their invaluable support in data collection. The authors would also like to thank Enago (http://www.enago.jp) for English language review.

**Funding** This work was supported by a Grant-in-Aid for Scientific Research (Nos. 17K11118, 17K11119, 17K16768, 17K16770, 17K167711, 18K16681, 18K16682, 18K16717, 18K16718, 18K16719, and 18K09157) from the Japan Society for the Promotion of Science.

## Compliance with ethical standards

**Conflict of interest** The authors have no conflict of interest.

## References

1. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol. 2013;14(13):1287–94. https://doi.org/10.1016/s1470-2045(13)70465-0.
2. Hutson TE, Al-Shukri S, Stus VP, Lipatov ON, Shparyk Y, Bair AH, et al. Axitinib versus sorafenib in first-line metastatic renal cell carcinoma: overall survival from a randomized phase III trial. Clin Genitourin Cancer. 2017;15(1):72–6. https://doi.org/10.1016/j.clgc.2016.05.008.
3. Pal SK, Signorovitch JE, Li N, Zichlin ML, Liu Z, Ghate SR, et al. Patterns of care among patients receiving sequential targeted therapies for advanced renal cell carcinoma: a retrospective chart review in the USA. Int J Urol. 2017;24(4):272–8. https://doi.org/10.1111/iju.13314.
4. Shinohara N, Abe T. Prognostic factors and risk classifications for patients with metastatic renal cell carcinoma. Int J Urol. 2015;22(10):888–97. https://doi.org/10.1111/iju.12858.
5. Tomita Y. Treatment strategies for advanced renal cell carcinoma: a new paradigm for surgical treatment. Int J Urol. 2016;23(1):13–21. https://doi.org/10.1111/iju.12899.
6. Lee JL, Kim MK, Park I, Ahn JH, Lee DH, Ryoo HM, et al. RandomizEd phase II trial of sunitinib four weeks on and two weeks off versus two weeks on and one week off in metastatic clear-cell type REnal cell carcinoma: restore trial. Ann Oncol. 2015;26(11):2300–5. https://doi.org/10.1093/annonc/mdv357.
7. Iwamoto K, Ishihara H, Takagi T, Kondo T, Yoshida K, Iizuka J, et al. Evaluation of relative dose intensity during the early phase of first-line sunitinib treatment using a 2-week-on/1-week-off

regimen for metastatic renal cell carcinoma. Med Oncol. 2018;35(6):78. https://doi.org/10.1007/s12032-018-1139-y.
8. Kawashima A, Uemura M, Kato T, Ujike T, Nagahara A, Fujita K, et al. Results of weekday-on and weekend-off administration schedule of sunitinib therapy for advanced renal cell carcinoma. Int J Clin Oncol. 2018. https://doi.org/10.1007/s10147-018-1332-1.
9. Mouillet G, Paillard MJ, Maurina T, Vernerey D, Nguyen Tan Hon T, Almotlak H, et al. Open-label, randomized multicentre phase II study to assess the efficacy and tolerability of sunitinib by dose administration regimen (dose modification or dose interruptions) in patients with advanced or metastatic renal cell carcinoma: study protocol of the SURF trial. Trials. 2018;19(1):221. https://doi.org/10.1186/s13063-018-2613-8.
10. Guida FM, Santoni M, Conti A, Burattini L, Savini A, Zeppola T, et al. Alternative dosing schedules for sunitinib as a treatment of patients with metastatic renal cell carcinoma. Crit Rev Oncol Hematol. 2014;92(3):208–17. https://doi.org/10.1016/j.critrevonc.2014.07.006.
11. Kondo T, Takagi T, Kobayashi H, Iizuka J, Nozaki T, Hashimoto Y, et al. Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma–comparison to standard dosing schedule of 4-weeks-on and 2-weeks-off. Jpn J Clin Oncol. 2014;44(3):270–7. https://doi.org/10.1093/jjco/hyt232.
12. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931–9. https://doi.org/10.1016/s0140-6736(11)61613-9.
13. Ambring A, Bjorholt I, Lesen E, Stierner U, Oden A. Treatment with sorafenib and sunitinib in renal cell cancer: a Swedish register-based study. Med Oncol. 2013;30(1):331. https://doi.org/10.1007/s12032-012-0331-8.
14. Eichelberg C, Vervenne WL, De Santis M, Fischer von Weikersthal L, Goebell PJ, Lerchenmuller C, et al. SWITCH: a randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. Eur Urol. 2015;68(5):837–47. https://doi.org/10.1016/j.eururo.2015.04.017.
15. Oya M, Tomita Y, Fukasawa S, Shinohara N, Habuchi T, Rini BI, et al. Overall survival of first-line axitinib in metastatic renal cell carcinoma: Japanese subgroup analysis from phase II study. Cancer Sci. 2017;108(6):1231–9. https://doi.org/10.1111/cas.13232.
16. Horiguchi H, Yoneyama T, Hatakeyama S, Tokui N, Sato T, Fujita N, et al. Impact of bacillus Calmette-Guerin therapy of upper urinary tract carcinoma in situ: comparison of oncological outcomes with radical nephroureterectomy. Med Oncol. 2018;35(4):41. https://doi.org/10.1007/s12032-018-1102-y.
17. Kido K, Hatakeyama S, Fujita N, Yamamoto H, Tobisawa Y, Yoneyama T, et al. Oncologic outcomes for open and laparoscopic radical nephroureterectomy in patients with upper tract urothelial carcinoma. Int J Clin Oncol. 2018. https://doi.org/10.1007/s10147-018-1248-9.
18. Momota M, Hatakeyama S, Tokui N, Sato T, Yamamoto H, Tobisawa Y, et al. The impact of preoperative severe renal insufficiency on poor postsurgical oncological prognosis in patients with urothelial carcinoma. Eur Urol Focus. 2018. https://doi.org/10.1016/j.euf.2018.03.003.
19. Hamano I, Hatakeyama S, Iwamurau H, Fujita N, Fukushi K, Narita T, et al. Preoperative chronic kidney disease predicts poor oncological outcomes after radical cystectomy in patients with muscle-invasive bladder cancer. Oncotarget. 2017;8(37):61404–14. https://doi.org/10.18632/oncotarget.18248.
20. Hosogoe S, Hatakeyama S, Kusaka A, Hamano I, Iwamura H, Fujita N, et al. Platinum-based neoadjuvant chemotherapy improves oncological outcomes in patients with locally advanced upper tract urothelial carcinoma. Eur Urol Focus. 2017:231–40. https://doi.org/10.1016/j.euf.2017.03.013.
21. Kodama H, Hatakeyama S, Fujita N, Iwamura H, Anan G, Fukushi K, et al. Preoperative chronic kidney disease predicts poor oncological outcomes after radical nephroureterectomy in patients with upper urinary tract urothelial carcinoma. Oncotarget. 2017;8(47):83183–94. https://doi.org/10.18632/oncotarget.20554.
22. Kubota Y, Hatakeyama S, Tanaka T, Fujita N, Iwamura H, Mikami J, et al. Oncological outcomes of neoadjuvant chemotherapy in patients with locally advanced upper tract urothelial carcinoma: a multicenter study. Oncotarget. 2017;8(60):101500–8. https://doi.org/10.18632/oncotarget.21551.
23. Kusaka A, Hatakeyama S, Hosogoe S, Hamano I, Iwamura H, Fujita N, et al. Detecting asymptomatic recurrence after radical cystectomy contributes to better prognosis in patients with muscle-invasive bladder cancer. Med Oncol. 2017;34(5):90. https://doi.org/10.1007/s12032-017-0955-9.
24. Koie T, Ohyama C, Okamoto A, Yamamoto H, Imai A, Hatakeyama S, et al. Presurgical therapy with axitinib for advanced renal cell carcinoma: a case report. BMC Res Notes. 2013;6:484. https://doi.org/10.1186/1756-0500-6-484.
25. Koie T, Ohyama C, Yoneyama T, Yamamoto H, Imai A, Hatakeyama S, et al. Feasibly of axitinib as first-line therapy for advanced or metastatic renal cell carcinoma: a single-institution experience in Japan. BMC Urol. 2015;15:32. https://doi.org/10.1186/s12894-015-0027-4.
26. Sheng X, Bi F, Ren X, Cheng Y, Wang J, Rosbrook B, et al. First-line axitinib versus sorafenib in Asian patients with metastatic renal cell carcinoma: exploratory subgroup analyses of Phase III data. Future Oncol. 2018. https://doi.org/10.2217/fon-2018-0442.
27. Tanaka Y, Hatakeyama S, Hosogoe S, Tanaka T, Hamano I, Kusaka A, et al. Presurgical axitinib therapy increases fibrotic reactions within tumor thrombus in renal cell carcinoma with thrombus extending to the inferior vena cava. Int J Clin Oncol. 2018;23(1):134–41. https://doi.org/10.1007/s10147-017-1169-z.
28. Hosogoe S, Hatakeyama S, Kusaka A, Hamano I, Tanaka Y, Hagiwara K, et al. Contrast media enhancement reduction predicts tumor response to presurgical molecular-targeting therapy in patients with advanced renal cell carcinoma. Oncotarget. 2017. https://doi.org/10.18632/oncotarget.17930.
29. Kim KH, Kim HY, Kim HR, Sun JM, Lim HY, Lee HJ, et al. Efficacy and toxicity of sunitinib in patients with metastatic renal cell carcinoma with renal insufficiency. Eur J Cancer. 2014;50(4):746–52. https://doi.org/10.1016/j.ejca.2013.11.029.
30. Choueiri TK, Larkin J, Oya M, Thistlethwaite F, Martignoni M, Nathan P, et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. Lancet Oncol. 2018;19(4):451–60. https://doi.org/10.1016/s1470-2045(18)30107-4.

## Affiliations

**Sakae Konishi[1] · Shingo Hatakeyama[1] · Toshiaki Tanaka[2] · Yoshinori Ikehata[3] · Toshikazu Tanaka[1] · Naoki Fujita[1] · Yusuke Ishibashi[1] · Hayato Yamamoto[1] · Takahiro Yoneyama[1] · Yasuhiro Hashimoto[1] · Kazuaki Yoshikawa[4] · Toshiaki Kawaguchi[5] · Naoya Masumori[2] · Hiroshi Kitamura[3] · Chikara Ohyama[1]**

Sakae Konishi
konishikosakana@gmail.com

Toshiaki Tanaka
zappa@pop12.odn.ne.jp

Yoshinori Ikehata
ikehata.y0226@gmail.com

Toshikazu Tanaka
yosage1205@yahoo.co.jp

Naoki Fujita
naonao707012@yahoo.co.jp

Yusuke Ishibashi
seirin1484@gmail.com

Hayato Yamamoto
yamahaya10@yahoo.co.jp

Takahiro Yoneyama
uroyone@hirosaki-u.ac.jp

Yasuhiro Hashimoto
bikkuri@opal.plala.or.jp

Kazuaki Yoshikawa
meatballdx@hotmail.com

Toshiaki Kawaguchi
toshiaki_kawaguchi@med.pref.aomori.jp

Naoya Masumori
masumori@sapmed.ac.jp

Hiroshi Kitamura
hkitamur@med.u-toyama.ac.jp

Chikara Ohyama
coyama@hirosaki-u.ac.jp

[1] Department of Urology, Hirosaki University Graduate School of Medicine, 5 Zaifu-chou, Hirosaki 036-8562, Japan

[2] Department of Urology, Sapporo Medical University School of Medicine, Sapporo, Japan

[3] Department of Urology, Graduate School of Medicine, University of Toyama, Toyama, Japan

[4] Department of Urology, Mutsu General Hospital, Mutsu, Japan

[5] Department of Urology, Aomori Prefectural Central Hospital, Aomori, Japan