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ORIGINAL ARTICLE

Changes in skeletal muscle area and lean body mass during pazopanib vs sunitinib therapy for metastatic renal cancer

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Abstract

Purpose To evaluate whether sunitinib and pazopanib treatments are associated with change in skeletal muscle area (SMA) and total lean body mass (LBM) as well as to compare their efficacies and safety profiles in patients with metastatic renal cell cancer (mRCC).

Methods Thirty-six patients treated with a tyrosine kinase inhibitor were included. Eighteen of them received sunitinib and the rest/remaining received pazopanib in the first line of mRCC treatment. Baseline and follow-up computed tomography studies of the patients were performed to measure cross-sectional areas (cm^2) of muscle tissues.

Results About 69% of patients were male and median age was 60 (49–68) years. Median time interval between two CT imagings was 6.1 (3.1–7.7) months and it was similar between the two groups (for sunitinib, 4.9 (2.5–6.9) months vs for pazopanib, 7.3 (3.2–9.5) months, $p=0.16$, respectively). Disease control rate was 77.7% in all patients. Of these, 66.6% in sunitinib group was consisted of four partial responses and eight stable diseases. In addition, 88.8% in pazopanib group was consisted of three partial responses and 13 stable diseases. A significant decrease in SMA and LBM was observed after sunitinib therapy, whereas SMA and LBM values of pazopanib group did not change significantly ($p=0.02$ and $p=0.70$, respectively). No significant differences were observed between patients with sunitinib, and pazopanib group median PFS [11.9 (95% CI 6.1–17.6) vs 8.1 months (95% CI 7.2–9.1), respectively; $p=0.28$] and median OS [28.6 (95% CI 24.3–32.9) vs 25.5 months (95% CI 18.9–52.7), respectively; $p=0.42$]. Dose-limiting toxicities were significantly more frequent in sunitinib group than in pazopanib group (66.7% vs 22.2%, $p=0.02$, respectively).

Conclusions Loss of SMA and LBM with sunitinib was more substantial than with pazopanib. Treatment efficacies of both drugs were similar, but dose-limiting toxicity was more frequent in sunitinib group. Loss of SMA had no significant association with prognosis. Further studies are needed to clarify the possible association between SMA and prognosis in mRCC patients who receive sunitinib or pazopanib.

Keywords Skeletal muscle area · Lean body mass · Sunitinib · Pazopanib · Renal cell cancer

Introduction

Renal cell carcinoma (RCC) comprises approximately 38% of all new cancers, with a median age of 64 years [1]. Approximately, 80% of RCCs have clear cell histology and other types include papillary, chromophobe, translocation and collecting duct tumors [2]. The 5-year survival for metastatic stage has increased from 7.3 to 11.7% [3].

Tyrosine kinase inhibitors (TKIs) as targeted therapy are widely used in the first- and second-line treatments of metastatic RCC. Pazopanib and sunitinib are oral angiogenesis inhibitors and act as multitargeted TKIs which are confirmed in phase I, II and III studies. These preferred agents were compared in a few studies, and briefly clinical efficacies of these were found to be similar, but they had different safety profiles.

During treatment of TKIs, muscle weakness is commonly encountered in routine oncology/clinical practice. Loss of

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skeletal muscle area (SMA) and total lean body mass (LBM) are associated with treatment toxicity and prognosis of various diseases [4–6]. To the best of our knowledge, there are no data about whether TKIs have an effect on SMA and LBM in the treatment of metastatic RCC patients. In this study, we aimed to assess whether sunitinib and pazopanib treatments are associated with a change in SMA and total LBM as well as to compare their efficacies and safety profiles in patients with mRCC.

Materials and methods

Study design

This was a retrospective and comparative study. Patients with mRCC who were admitted to Trakya University Medical Oncology between 2010 and 2017 were included in this retrospective study. The medical records of 72 patients with mRCC were evaluated and 36 of them who had computed tomography (CT) scanning before and during sunitinib or pazopanib treatment were eligible (Fig. 1). All patients had histologically proven metastatic RCC.

Treatment regimens

All of the patients were treated with a tyrosine kinase inhibitor. Eighteen of them received sunitinib and the remaining received pazopanib in the first line of mRCC treatment. Pazopanib was received orally at a once-daily dose of 800 mg, with continuous dosing. Sunitinib was administered orally in 6-week cycles at a once-daily dose of 50 mg for 4 weeks, followed by 2 weeks without treatment.

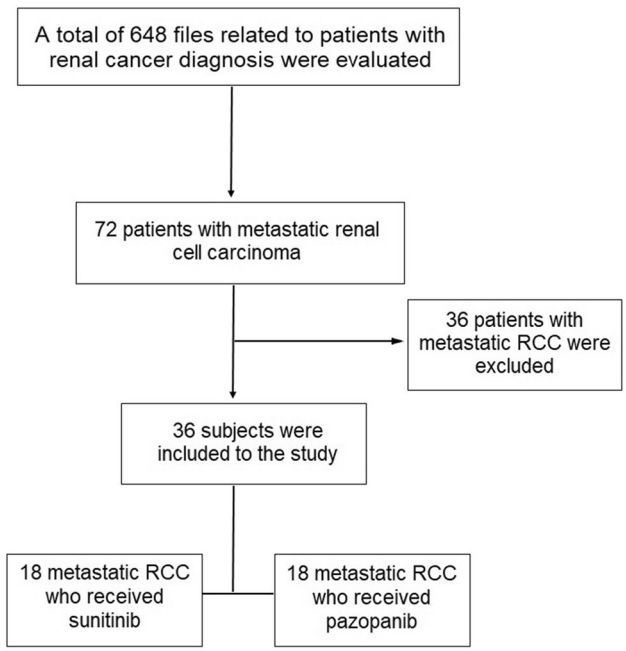

Fig. 1 Patients' selection method

CT imaging

Baseline and follow-up CT studies of the patients were performed (Aquillon, 64- detector, Toshiba Medical Systems, Tokyo, Japan) and the CT parameters found to be as follows: gantry rotation time 0.5 s, section collimation 0.5 mm, helical pitch 53, 125 mAs, and 120 kVp. CT images which were performed at the diagnosis and follow-up during treatment period before progression were used for analysis. To measure the cross-sectional areas of SMA, L3 was set as a landmark [7], and muscles were identified based on their anatomic features, and the structure of those specific muscles was quantified based on pre-established thresholds of skeletal muscle tissue [8]. Cross-sectional areas (cm^2) of muscle tissues were computed for each image. The total lumbar–skeletal muscle cross-sectional area is linearly related to the whole-body muscle and the total LBM was estimated from muscle cross-sectional areas as described by Mourtzakis et al. [9]: LBM (kg) = (0.30 × [SMA at L3 using CT (cm^2)] + 6.06). These images were evaluated by the radiologist who was blind about treatment groups and had 13 years (EY) of abdominal imaging experience.

Statistical analysis

Data were presented as mean ± standard deviation, minimum and maximum. Categorical variables were reported as frequencies and group percentages. Change from baseline SMA and total LBM were summarized by median (25th–75th inter quartile range). Change from baseline was tested by signed rank test. OS was estimated using the Kaplan–Meier product limit method. A p value less than 0.05 was considered as statistically significant.

Results

Study patients

Baseline demographic and clinical characteristics of the patients are shown in Table 1. The study subjects of sunitinib group were similar to pazopanib group. In brief, 69.4% were male with a median age of 60 (49–68) years. ECOG performance status of all patients ranged between 0 and 2 and the majority of the patients (80.6%) had clear cell pathology. The most common metastatic site was lung and time from diagnosis to treatment was similar between sunitinib and pazopanib groups. On the other hand, median time interval between two CT imagings was 6.1 (3.1–7.7)

Table 1 Demographic and clinical characteristics of the study subjects

	All ($n=36$)	Sunitinib group ($n=18$)	Pazopanib group ($n=18$)
Age, years			
Median (IQR)	60 (49–68)	58 (48–62)	61 (50–69)
Gender, F/M	11/25	4/14	7/11
Eastern Cooperative Group, *n*%			
0	21 (58.3)	11 (61.1)	10 (55.6)
1	13 (36.1)	6 (33.3)	7 (38.9)
2	2 (5.6)	1 (5.6)	1 (5.6)
Histopathology, *n*%			
Clear cell	29 (80.6)	15 (83.3)	14 (77.8)
Papillary	7 (19.4)	3 (16.7)	4 (22.2)
MSKCC group, *n*%			
Low risk	2 (5.6)	1 (5.6)	1 (5.6)
Intermediate risk	28 (77.8)	15 (83.3)	13 (72.2)
High risk	6 (16.7)	2 (11.1)	4 (22.2)
Nephrectomy, *n*%	32 (88.8)	17 (94.4)	12 (80.0)
Specific metastatic site, *n*%			
Lung	23 (63.8)	12 (66.6)	11 (61.1)
Bone	14 (38.8)	8 (44.4)	6 (33.3)
Liver	3 (8.3)	1 (5.5)	2 (11.1)
Brain	3 (8.3)	2 (11.1)	1 (5.5)
Metastatic site, *n*%			
1	20 (55.5)	10 (55.5)	10 (55.5)
2	16 (44.4)	8 (44.4)	8 (44.4)
Time from diagnosis to treatment			
Median (IQR)	2.5 (1.5–5.3)	3.9 (1.6–6.0)	2.1 (1.1–5.0)
DCR at the first radiological evaluation, *n*%	28 (77.7)	12 (66.6)	16 (88.8)
Baseline skeletal muscle area at L3 vertebra level (cm^2)			
Median (IQR)	158.5 (138.1–179.1)	172.9 (138.1–184.1)	152.2 (134.1–178.3)

DCR disease control rate, *IQR* interquartile range, *MSKCC* Memorial Sloan Kettering Cancer Center

months and it was similar between the two groups [for sunitinib, 4.9 (2.5–6.9) months vs for pazopanib, 7.3 (3.2–9.5) months, $p=0.16$, respectively].

Total lean body mass and skeletal muscle area

Baseline LBM values were similar in both groups. A significant decrease in LBM was observed after sunitinib therapy, whereas LBM values of pazopanib group did not change significantly ($p=0.02$ and $p=0.68$, respectively; Fig. 2). Table 2 shows that the change in LBM values between baseline and after the start of sunitinib therapy was significant ($p=0.02$). Similarly, baseline SMA values were similar in both groups. A significant decrease in SMA was observed after sunitinib therapy, whereas SMA values of pazopanib group did not change significantly ($p=0.02$ and $p=0.68$, respectively; Table 2).

Treatment tolerability

Table 3 shows the treatment-related toxicities in both groups. Overall, 15 (44.4%) patients experienced a dose-limiting toxicity. Baseline SMA was not related to DLT [median SMA = 158.1 (patients who had DLT: 136.2–184.5 vs patients who had no DLT: 160.4 (138.1–176.4), $p=0.74$]. DLT was significantly much more in sunitinib group rather than pazopanib group (66.7% vs 22.2%, $p=0.02$, respectively). All patients who had DLT required dose reduction and there was not any early cessation or delay of treatment due to toxicity. Fatigue was significantly higher in sunitinib (75%) group than in pazopanib (45%) group ($p=0.04$). The most common adverse events were dermatological findings (pruritus/rash, hand–foot syndrome) in both groups and there was a trend towards more hemotological toxicities in sunitinib group (41.6% vs 27.7%, $p=0.09$).

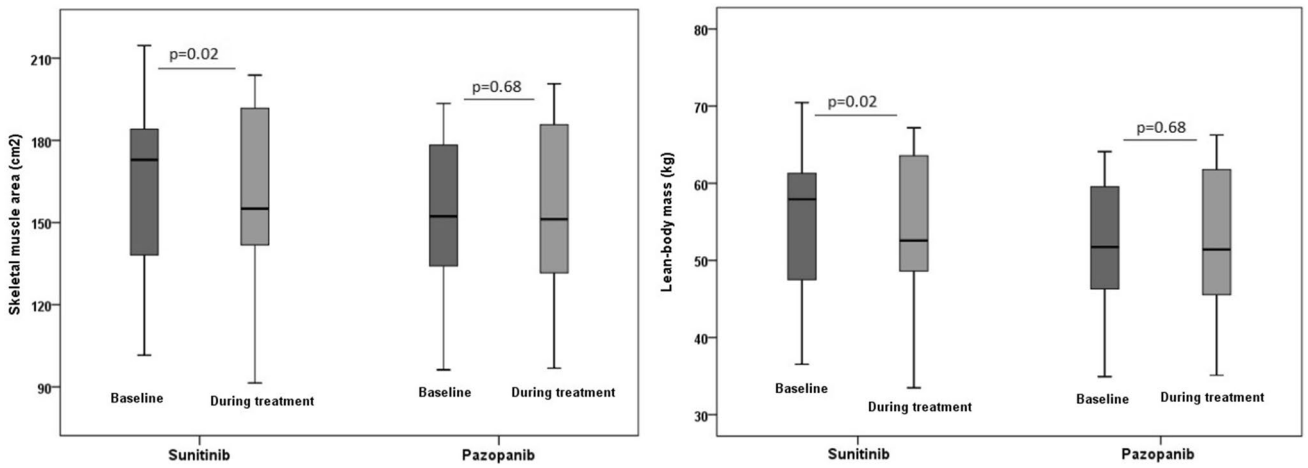

Fig. 2 SMA and LBM changes during sunitinib and pazopanib treatment

Table 2 SMA and LBM changes after sunitinib and pazopanib in patients with mRCC

	Sunitinib group ($n=18$)	Pazopanib group ($n=18$)	p value
Baseline			
SMA median (IQR), (cm^2)	172.9 (138.1–184.1)	152.2 (134.1–178.3)	0.24
LBM median (IQR), (kg)	57.9 (47.5–61.3)	51.7 (46.3–59.5)	
During treatment			0.25
SMA median (IQR), (cm^2)	155.1 (141.8–191.7)	151.2 (131.6–185.7)	
LBM median (IQR), (kg)	52.5 (48.6–63.6)	51.4 (45.5–61.7)	
Change in SMA value			**0.02**
SMA median (IQR), (cm^2)	6.8 (1.2–10.1)	−2.8 (−4.1 to 1.0)	
LBM median (IQR), (kg)	5.6 (1.2–10.1)	−0.3 (−4.1 to 1.0)	
p value	**0.02**	0.68	

Bold—p value < 0.05

LBM lean body mass, *SMA* skeletal muscle area

Survival outcome

Disease control rate was 77.7% in all patients, and it was similar in both groups ($p=0.22$). In sunitinib group, partial response rate was 22% (4 patients) and stable disease rate was 44.4% (8 patients). In pazopanib group, partial response was 16.7% (3 patients) and stable disease rate was 72.2 (13 patients). On the other hand, the median PFS and OS for the study population ($n=36$) were 10.2 (95% CI 5.6–14.9) and 28.6 months (95% CI 19.9–37.8), respectively. Baseline SMA was not significantly associated with PFS or OS ($p=0.46$ vs $p=0.36$, respectively). No significant differences were observed between patients in sunitinib, and pazopanib groups median PFS [11.9 (95% CI 6.1–17.6) vs 8.1 months (95% CI 7.2–9.1), respectively; $p=0.28$] and median OS [28.6 (95% CI 24.3–32.9) vs 25.5 months (95% CI 18.9–52.7), respectively; $p=0.42$]. When considering patients who had decreased LBM and those who had non-decreased LBM patients, no significant differences were observed regarding PFS ($p=0.70$) or OS ($p=0.28$).

Discussion

Targeted therapy for mRCC is widely used in the first- and second-line settings. Pazopanib and sunitinib are preferred options for treatment of mRCC and have different safety profiles. In this study, we revealed that sunitinib therapy significantly resulted in higher loss of SMA and total LBM compared to pazopanib therapy, although baseline SMAs and total LBMs were similar. In addition, dose-limiting toxicities were higher in sunitinib group, whereas disease control rates, PFS and OS were comparable in both groups.

Loss of SMA is generally associated with higher incidence of treatment-related toxicity and mortality in different clinical diseases [4, 5]. Importantly, it is demonstrated that lower skeletal muscle index has prognostic significance in

Table 3 Dose-limiting toxicity and the adverse event profile during treatment

	Sunitinib group ($n=18$)	Pazopanib group ($n=18$)	p value
DLT, n (%)	12 (66.7)	4 (22.2)	0.02
Mucositis, n (%)			
Grade 1–2	8 (44.4)	7 (38.8)	0.67
Hypertension, n (%)			
Grade 1–2	7 (38.8)	8 (44.4)	0.11
Hand–foot syndrome, n (%)			
Grade 1–2	7 (38.8)	6 (33.3)	0.68
Hypothyroidism, n (%)			
Grade 1–2	8 (44.4)	2 (11.1)	0.21
Dermatologic, n (%)			
Pruritus/rash, Grade 1–2	6 (33.3)	5 (27.7)	0.69
Proteinuria, n (%)			
Grade 1–2	2 (11.1)	4 (22.2)	0.17
Liver transaminase increase, n (%)			
Grade 1–2	4 (22.2)	1 (5.5)	0.33
Neutropenia, n (%)			
Grade 1–2	4 (22.2)	0	0.09
Grade 3	1 (5.5)	0	
Anemia, n (%)			
Grade 1–2	8 (44.4)	7 (38.8)	0.97
Thrombocytopenia, n (%)			
Grade 1–2	2 (11.1)	1 (5.5)	0.42
Grade 3	0	1 (5.5)	

patients with solid tumors [5, 6]. This association between sarcopenia and malignancy might vary among different solid tumors and according to the severity of disease and its importance for mRCC is still unclear [5]. First, the prognostic significance of sarcopenia in patients with mRCC had shown an association with drug toxicity only. Antoun et al. showed that mRCC patients with baseline sarcopenia had more dose-limiting toxicities with sorafenib treatment [7]. In addition, Huillard et al. revealed that mRCC patients with baseline sarcopenia experienced significantly more dose-limiting toxicities during the first cycle of sunitinib treatment [10]. These studies were not significantly associated with PFS or OS, but Fukushima et al. demonstrated that baseline sarcopenia was a significant prognostic factor of mRCC [11]. In these studies, only baseline SMA was significantly associated with drug toxicity. Compared to our study, we showed that baseline SMA was not associated with DLT and prognosis (PFS or OS). Interestingly, baseline SMA and LBM were significantly reduced with sunitinib therapy compared to pazopanib therapy without progression of disease. To exclude bias of disease progression, the measurement of SMA and total LBM during treatment interval was obtained before CT imagings that show disease progression.

Receptor tyrosine kinases, (EGFR, VEGFR, etc.) can also mediate cancer proliferation and angiogenesis [12]. One of the most important issues for tumor growing beyond 1–2 mm^3 is angiogenesis which is controlled by anti- and pro-angiogenic factors. In cancer, tumor angiogenesis switch the angiogenic balance towards downregulation of anti-angiogenic factors and upregulation of pro-angiogenic tumor factors [13]. Sunitinib is a multitargeted tyrosine kinase inhibitor, has antitumor and anti-angiogenic activities due to inhibition of PDGFRa,-b; KIT; VEGFR-1,-2-3; FLT3; CSF1R and RET has 10–30 times more potent effect against PDGFR andVEGFR2 [14, 15]. Its high antitumor activity has been confirmed in phase I, phase II and phase III studies, with significant disease control rate. In a phase II trial, Motzer et al. showed that disease control rate was 67.% and then, they showed that objective response rate was 31% with sunitinib against interferon alfa as first-line therapy in a phase III study [16–20]. On the other hand, pazopanib is another multityrosine kinase inhibitor, has anti-angiogenic properties through inhibition of VEGFR-1, -2, and -3, interleukin-2 receptor-inducible T-cell kinase, leukocyte-specific protein tyrosine kinase, PDGFR-α and -β, stem cell factor receptor, transmembrane glycoprotein receptor tyrosine kinase and fibroblast growth factor receptors 1 and 3 [20]. COMPARZ study revealed that pazopanib had similar efficacy and was more favorable in terms of safety and quality-of-life profiles compared to sunitinib [20]. Investigator-assessed disease control rate was 74% in pazopanib group and 70% in sunitinib group [20]. In our study, the results were consistent with the literature, disease control rate was 77.7% in all patients, and it was similar in both groups (66.6% in sunitinib group vs 88.8% in pazopanib group, $p=0.22$).

A systematic review showed that sunitinib, sorafenib, axitinib, pazopanib and bevacizumab (known as the first-line antiangiogenetic agents) for mRCC had similar efficacy with different safety profiles [21]. Especially, in a few studies, pazopanib was compared to sunitinib in the treatment of mRCC [20, 22]. Briefly, pazopanib and sunitinib had beneficial effects for patients with metastatic RCC with similar efficacy, but patients favored pazopanib over sunitinib due to the toxicity profiles and quality of life (QoL) scores [20, 22–27]. Moreover, it is known that one-third of mRCC patients who received sunitinib had muscle weakness and limb pain. But there are no data regarding total LBM and SMA in known profiles of each drug. In our study, we revealed that loss of SMA and total LBM in patients with sunitinib treatment was higher than in those with pazopanib treatment. To the best of our knowledge, our results are first to demonstrate this difference. The reason for this difference is unclear. In addition, molecular mechanisms of muscle wasting might be related to protein kinases and higher muscle loss may be attributed to their different kinase selectivities [28]. Sunitinib was shown

to inhibit more kinases than pazopanib [29]. More multikinase inhibition appears to be associated with more toxicities thus leading to more loss of SMA than pazopanib. However, it would be very difficult to differentiate specific adverse effects of multikinase inhibitors owing to the complexity of protein kinase signaling pathways. Another possible explanation is that sunitinib might induce NF-KB activation and augment expression of IL-6, IL-8 and TNF-alpha [30]. TNF-α is the main inflammatory cytokine that induces a transcription factor and contributes to the loss of muscle mass along IL-6, and it has been suggested that the tumor has a great influence on the increasing levels of these factors in the circulation [31, 32]. In fact, it has been demonstrated that TNF-α acts more on type II fibers to stimulate apoptosis signaling. In addition, TNF-α stimulates the activation and nuclear translocation of NF-kB in skeletal muscle cells, which contributes to muscle catabolism [31]. On the other hand, Spirina et al. showed that pazopanib decreases the levels of NF-κB, p65 and p50 levels in patients with RCC [33]. In addition, Ishibashi et al. revealed that pazopanib treatment leads to less phosphorylation of NFκB, STAT3 and mTOR as well as HIF expression compared to sunitinib and sorafenib treatments [34]. Treatment-induced lower IL-6 and IL-8 levels were also identified with pazopanib treatment in patients with RCC [35]. These differences might explain the reason why sunitinib induced skeletal muscle loss much more than pazopanib. To clarify this possible relation, more detailed studies are required.

Different safety profiles of the tyrosine kinase inhibitors have important effect on choosing treatment option for disease management. As far as tolerability is concerned, patients treated with sunitinib showed a higher incidence of diarrhea, vomiting, hypertension, hand–foot syndrome, and neutropenia [20]. On the other hand, it was shown that patients who received pazopanib had higher quality of life (QoL) scores than the ones who received placebo [36]. The PISCES study revealed that patients who received pazopanib had less fatigue and better overall QoL, with less diarrhea. We also found that patients who received sunitinib had higher fatigue symptoms than patients who received pazopanib [22]. In addition, COMPARZ study also demonstrated that common adverse events of any grade were reported more frequently with sunitinib than with pazopanib [20]. The conclusion drawn from the COMPARZ and the PISCES studies was that patients favored pazopanib over sunitinib due to toxicity and QoL score [20, 22]. Moreover, Motzer et al. showed that dose reductions and treatment interruptions were similar between pazopanib and sunitinib [20]. In our study, more profound concern about toxicity is fatigue in both groups and DLT was higher in sunitinib group than pazopanib group. All patients who had DLT continued their treatment and there was no interruption of treatment. In addition, other common adverse events with sunitinib treatment were mucositis, hand–foot syndrome, cutaneous findings, hypertension, anemia, hypothyroidism and increased liver transaminase level, similar to those with pazopanib treatment. These adverse events of the both drugs were consistent with each drug's known profile, but pazopanib proved to be superior to sunitinib in terms of protection of SMA and total LBM.

Some major limitations should be considered. First of all, retrospective clinical data based on the medical records of patients with RCC bring some disadvantages in the assessment of treatment-related symptoms and adverse events. Second, the study was made on a small number of patients. In addition, SMA and total LBM measurements were performed twice: at baseline and under treatment. All measurements were recorded only from the CT imagings before progression during achieved disease control. There were no data on the change in QoL scores in the baseline and under treatment. Furthermore, the toxicity profiles might have been prepared with incomplete data, because it is not possible to take all adverse events into consideration in a retrospective study. Despite these limitations, it has been an outstanding strength of the study to conclude that sunitinib therapy significantly resulted in higher loss of SMA and total LBM compared to pazopanib therapy. We suggest that our results give an opinion to treat more fragile mRCC patients to prevent muscle loss during first-line setting.

In conclusion, loss of SMA and LBM with sunitinib was more than with pazopanib. Treatment efficacies of both drugs were similar, but dose-limiting toxicity was more frequent in sunitinib group. Loss of SMA had no significant association with prognosis. Further studies are needed to clarify the possible association between SMA and prognosis in mRCC patients who receive sunitinib or pazopanib.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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