Clinical Case Report

Medicine®

OPEN

Sunitinib rechallenge with dose escalation in progressive metastatic renal cell carcinoma

A case report and literature review

Xingming Zhang, MD[a], Pengfei Shen, MD[a], Jin Yao, MD[b], Ni Chen, MD, PhD[c], Jiyan Liu, MD, PhD[d], Hao Zeng, MD, PhD[a,*]

Abstract

Rationale: We aimed to present a case of sunitinib rechallenge with dosage escalation after disease progression, hopefully, providing an optional approach to the personalized medication management of progressive metastatic renal cell carcinoma (mRCC).

Patient concerns: The patient was admitted to hospital due to right kidney mass, with merged enlargement of retroperitoneal lymph nodes. Subsequent surgery and sunitinib treatment was administered.

Diagnoses: Postoperative pathologic diagnosis was type II papillary renal cell carcinoma (pRCC) (Fuhrman grade 3) with metastases of retroperitoneal lymph nodes (T1aN1M0).

Interventions: The patient underwent cytoreductive nephrectomy followed by treatment of sunitinib standard therapy (4/2 schedule) and alternative schedules according to different disease status. The patient received alternative 2/1 schedule while experiencing grade 3/4 adverse events. Re-challenge with sunitinib upon disease progression and metastasectomy were given. After second disease progression, sunitinib rechallenge with dose escalation was administered. Around 2/1 schedule showed desirable efficacy and better tolerance.

Outcomes: After 4 months of sunitinib individualized treatment, a complete response with retroperitoneal metastases was achieved. Rechallenge with sunitinib after disease progression and also rechallenge with dose escalation after second disease progression were effective.

Lessons: Cessation of sunitinib in patients with complete response is not suggested. Also, strategy of subsequently administered sunitinib after metastasectomy is seemed to be effective. What is more, sunitinib rechallenge with escalation to 62.5 mg probably possess value in progressive mRCC and has a well tolerance when sunitinib is rechallenged. Based on this case, we probe a feasible alternative strategy in personalized therapy of sunitinib, hoping for providing referable insights into the detailed strategies of individual treatment for patients with mRCC.

Abbreviations: AE = adverse event, CN = cytoreductive nephrectomy, mRCC = metastatic renal cell carcinoma, mTOR = mammalian target of rapamycin, pRCC = papillary renal cell carcinoma, TKI = inhibiting tyrosine kinases receptors, VEGF = vascular endothelial factor.

Keywords: dose escalation, metastatic renal cell carcinoma, progressive, rechallenge, sunitinib

Editor: N/A.

XZ and PS are the co-first authors and contributed equally to this study.

Conflicts of Interest and Source of Funding: This work was supported by Natural Science Foundation of China (NSFC 81402110 and 81672547), Science and Technology Support Program of Sichuan Province (2015SZ0230-3) and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (No.0040205301E21). The authors declare that they have no competing interests.

Ethics approval and consent to participate: Ethical approval was not required for this case report; however, the patient gave written informed consent for publication and use of all accompanying images.

The authors have no conflicts of interest to disclose.

[a] Department of Urology, Institute of Urology, [b] Department of Radiology, [c] Department of Pathology, [d] Department of Oncology, West China Hospital, Sichuan University, Chengdu, China.

[*] Correspondence: Hao Zeng, Guoxue Xiang 37#, Chengdu, China, 610041 (e-mail: kucaizeng@163.com).

Medicine (2018) 97:31(e11565)

Received: 31 March 2018 / Accepted: 27 June 2018

http://dx.doi.org/10.1097/MD.0000000000011565

1. Introduction

Significant breakthroughs about the treatment of metastatic renal cell carcinoma (mRCC) have been achieved by blocking pathways of vascular endothelial factor (VEGF) and mammalian target of rapamycin (mTOR). Involving in the process of inhibiting tyrosine kinases receptors (TKI), sunitinib is suggested taking orally at a dose of 50 mg/day (4 weeks on and 2 weeks off, 4/2 schedule), in spite of other studies developed as continuous administration and 2/1 schedule (2 weeks on and 1 week off).[1]

Nevertheless, resistance almost inevitably arises in sunitinib-treated patients. Despite of unclearness of resistance and undefined efficacy of sequential or combined therapies, sequential treatment using other small molecular drugs is considered as an accepted approach.[2] Given the fact that, whereas, reuse of the same therapy has been proved to be responsive in acquired drug resistance, and several alternatives have been applied to patients who have progressed or who are at relapse.[3,4]

We present a case of sunitinib rechallenge with dosage escalation after disease progression, hopefully, providing an optional approach to the personalized medication management of progressive mRCC.

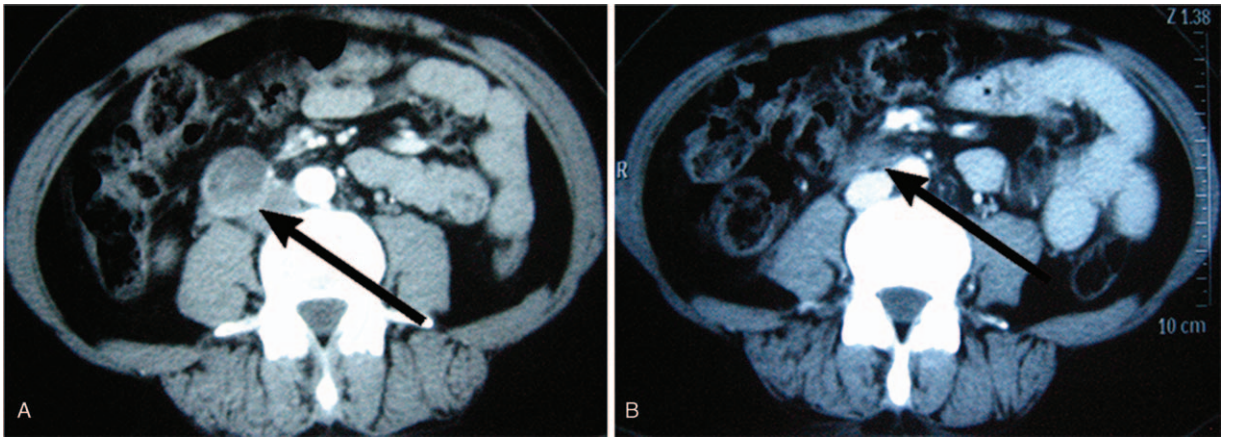

Figure 1. Constructed CT scans before starting sunitinib and after 2 months of 4/2 schedule and 4 months of 2/1 schedule. (A) After the first surgery before starting sunitinib. (B) Achievement of complete response (CR) after 2 months of 4/2 schedule and 4 months of 2/1 schedule. CR = complete response.

2. Case report

A 38-year-old female was admitted to hospital due to right kidney mass (18×15 mm), with merged enlargement of retroperitoneal lymph nodes (located at the front of inferior vena cava at the level of lower polar of right kidney, 36 × 28 mm) indicated by computed tomography (CT). Based on a good status of the patient (Karnofsky performance status 90, lactate dehydrogenase 118 IU/L, hemoglobin 129 g/L, corrected calcium 2.27 mmol/L), cytoreductive nephrectomy (CN), and incomplete lymphadenectomy were performed. Postoperative pathology was type II papillary renal cell carcinoma (pRCC) (Fuhrman grade 3) with metastases of retroperitoneal lymph nodes (T1aN1M0).

After 1 month (Fig. 1A), sunitinib was administered in standard 4/2 schedule. Within 2 cycles, grade 3/4 adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE)—hypertension, hand-foot syndrome and general edema—were observed. Therefore, individualized regimen of 2/1 schedule was recommended. After 4 months, a complete response (CR) with retroperitoneal metastases was achieved (Fig. 1B). About 42 months later, the patient discontinued sunitinib without urologist's permission.

Active monitoring was performed and the tumor was stable until 18 months after cessation of sunitinib, when CT scan indicated recurrent enlargement of retroperitoneal lymph nodes (20 × 23 mm, Fig. 2A). So, sunitinib was given once again at 50 mg in 2/1 schedule for 6 weeks, and following CT presented small shrinkage of the tumor (17 × 23 mm, Fig. 2B). Then, the patient accepted an additional metastasectomy in the light of a multidisciplinary team (MDT), which was consisted of urologists, radiologists, pathologists, and oncologists.

Tumors were incompletely resected again duo to extreme contiguity to left renal vein, vena cava and aorta. Postoperative medication was continuously taken sunitinib with the same schedule as the initial (Fig. 3A). However, the enlarged lymph nodes increased from 18 × 19 to 22 × 28 mm about 3 months later (Fig. 3B). Therefore, elevation of sunitinib to 62.5 mg was considered, and a shrink of the metastasis (18 × 22 mm) was observed after another 3 months (Fig. 3C). Hitherto, CT scan was performed every 3 months and tumors were stable (22 × 23 mm,

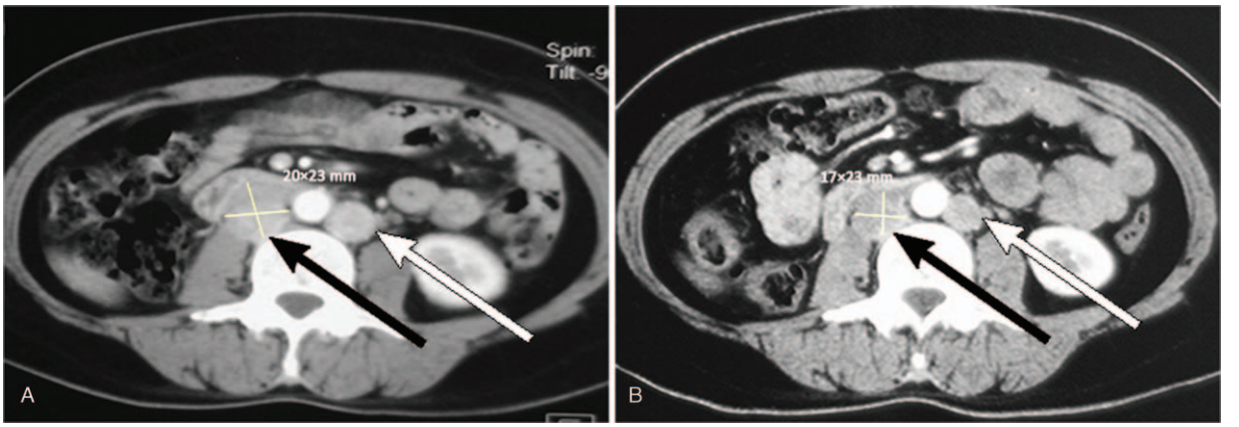

Figure 2. Constructed CT scans of recurrence and after sunitinib rechallenged. (A) Recurrent enlargement of retroperitoneal lymph nodes. The largest one was 20×23 mm (red arrow), another obvious one between aorta and left renal vein (blue arrow). (B) Contrasted CT scan after 2 cycles of regaining sunitinib with 2/1 schedule showed small shrinkage of the tumor, indicating stable disease (SD) was achieved. SD = stable disease.

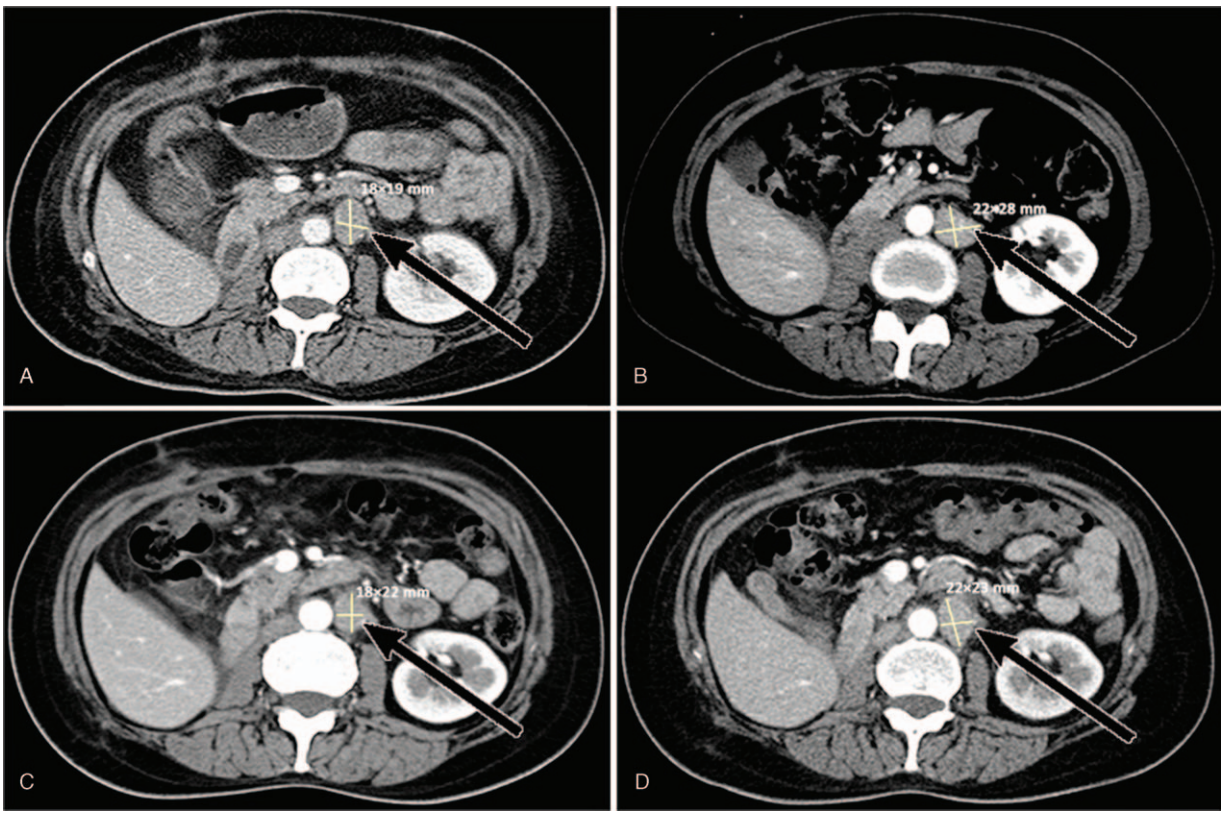

Figure 3. Contrasted CT scans during sunitinib rechallenge therapy after the second surgery. (A) Baseline of sunitinib rechallenge with 50 mg in standard schedule. (B) The patient had a progression disease 3 months after the second surgery, and the tumor size was 22×28 mm. (C) A shrinkage was detected after 2 cycles of sunitinib elevating to 62.5 mg (18×22 mm). (D) The latest CT scan showed the metastatic lymph nodes were stable about 12 months after elevation of sunitinib to 62.5 mg (22×23 mm).

Fig. 3D). The management procedures were shown in Figure 4. In addition, during the time of sunitinib rechallenge with dose escalation, the patient was well tolerable, with AEs under grade 3.

3. Discussion

Since sorafenib has been approved by the US FDA as a standard treatment of mRCC in 2005, the survival outcomes of mRCC patients have been significantly improved.[5] Despite several targeted drugs have been successively approved to treat mRCC, the proportion of CR is yet <15%, and drug resistance may inevitably occur after 5.5 to 14 months of treatment. In clinical practice, whether targeted treatment should be discontinued after the patient achieved CR still remains controversy,[6] and there is no enough evidence supporting a standard targeted drug to treat patients with metastatic nonclear cell RCC. In 2009, Johannsen et al retrospectively reviewed 12 mRCC patients who achieved CR after TKI treatment and found that 58.3% (7/12) of them remained stable disease after treatment cessation. On the contrary, however, 41.7% (5/12) of the patients developed progression disease, and among them, 3 patients developed new lesions.[7] It was noteworthy that one from the 3 patients occurred spinal cord compression within 3 months after treatment cessation. Since the small sample size and short follow-up time (median 8.5 months), the results of this study were not enough to answer the question that whether the drug should be discontinued. Subsequently, a larger retrospective study reported that withdrawal of TKI after CR seemed feasible, as readministration of the original drug when disease progression was also effective, and discontinuation of TKI improved patient's quality of life and reduced patient's cost.[6] In general, however, 37% to 80% of patients with CR and discontinuation of TKI occurred disease progression, and 32% to 77% of them developed new lesions.[6–11] At the same time, patients who immediately discontinued treatment after CR experienced a significantly higher rate of disease progression than those who received a short term of treatment and continuous treatment after having achieved CR (44%, 13%, and 13%, respectively).[6] More importantly, although the majority of patients (70%) remained to respond to the original TKI drug after disease progression, multivariate analysis showed that, compared with those without disease progression, patients with disease progression after treatment discontinuation were more likely to develop death and the risk of death increased 31.4% (HR 3.18, 95% CI 1.48–6.83, $P = .0005$).

Since most renal cancers are clear cell RCC, further work is needed in exploring the efficacy of targeted drugs in patients with nonclear cell RCC. Although the overall survival (OS) of patients with nonclear cell RCC were shorter than that of clear-cell RCC, the median progression-free survival (PFS) and OS of patients with non-clear cell RCC were 1.6 to 11.9 months and 10.8 to 25.6 months, respectively, indicating that targeted drugs were still effective in selected nonclear cell RCC patients.[12,13] Although there is not enough evidence to support the efficacy of sunitinib monotherapy in nonclear RCC, its potential

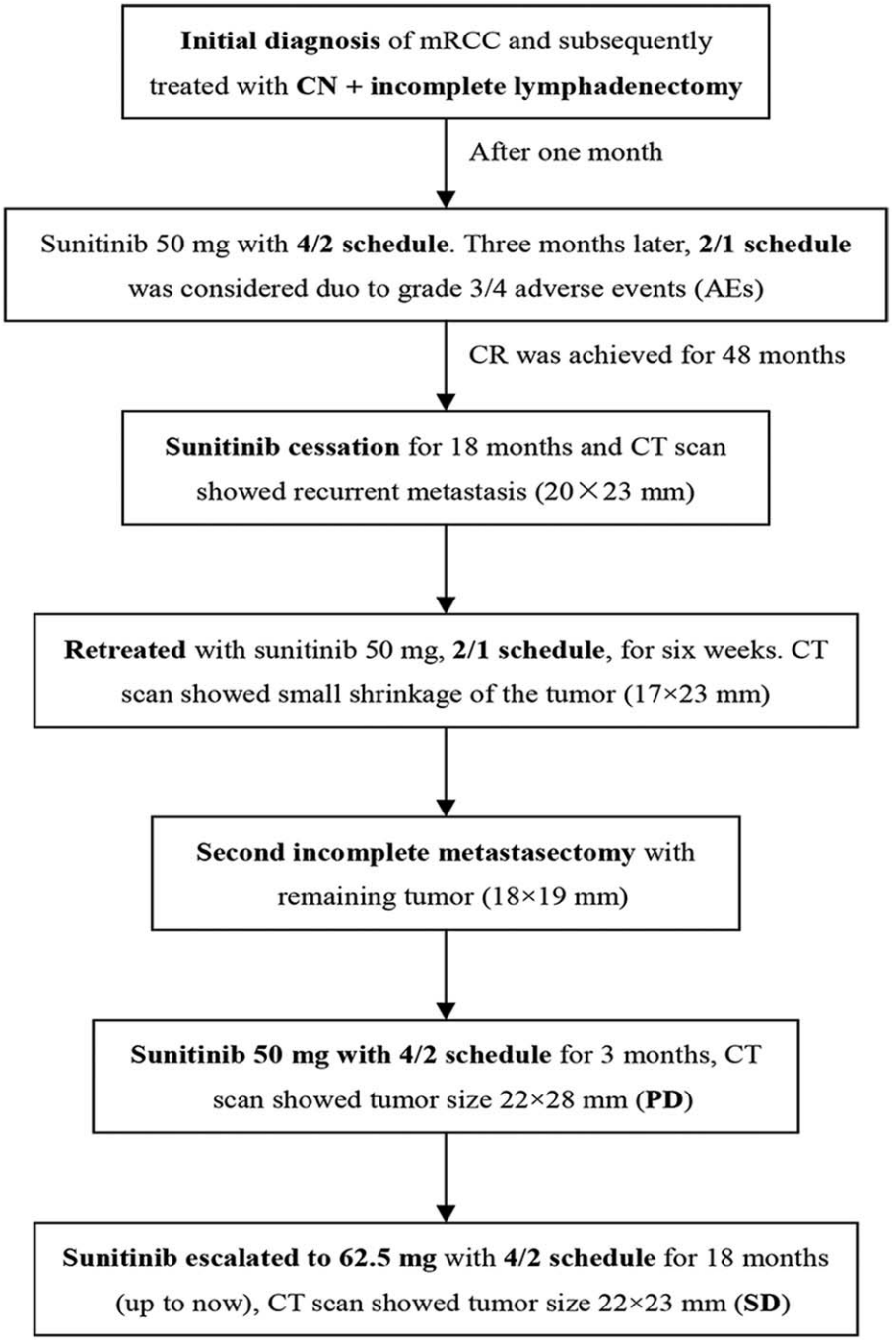

Figure 4. The flow diagram of the management. CN = cytoreductive nephrectomy, CR = complete response, PD = progression disease, SD = stable disease.

therapeutic effect should not be overlooked. In the present case report, severe drug-related adverse events (AEs) indirectly demonstrated the therapeutic effect of sunitinib. In addition, the long 6-year survival time in this case further demonstrated the effectiveness of individualized treatment strategies.

Patients with mRCC would inevitably occur drug resistance after a period of treatment. Sequential and combined treatment of targeted drugs are the mainstay of treatment in patients with refractory mRCC.[14] Rechallenge of the original drug after disease progression has become a potential solution.[3] Although the current researches on sunitinib rechallenge were designed as retrospective cohort or included small sample sizes, all results suggested that the drug resistance of sunitinib might be mediated by a transient mechanism which could be reversed by re-using the original drug and/or increasing the dose of the drug.[15,16] Meanwhile, both the objective response rate (ORR) and median PFS in patients who received sunitinib rechallenge were similar to those who were sequentially treated with other targeted drugs.[3,17,18] In addition, both clinical and laboratory studies confirmed that increasing drug doses reversed sunitinib resistance.[4,16] However, no study reported sunitinib rechallenge with dose escalation in mRCC. The present case report suggested that the combination of rechallenge and dose escalation seems to be feasible in reversing transient resistance. On top of that, it

should be noted that the relationship between AEs and efficacy should be balanced when considering dose escalation in clinical practice. In the present case, no additional AEs were observed. SWITCH studies showed that sorafenib-sunitinib group is more tolerant than sunitinib-sorafenib group.[19] This result suggested that sunitinib as a prestimulus which enhanced patient's tolerance. The results of a randomized controlled trial further confirmed the conclusion that patients' tolerance to AEs were also enhanced as the dose of targeted drug was increased.[20] However, some patients may experience grade 1 or 2 AEs, while others may experience grade 3–4 AEs. Therefore, sunitinib dose escalation should be considered only if there was no grade 3–4 AEs. In contrast, grade 1–2 AEs were potential hints for dose escalation and physicians are required to make decisions with patients.

Although the resection of metastases is still controversial, it still plays an important role in the treatment of mRCC. The patient has survived more than 8 years, postoperative disease control is also impressive. One study reported that patients who underwent complete resection of metastases had longer median cancer-specific survival than those who received incomplete resection (4.8 and 1.3 years, respectively).[21] However, the disease developed rapidly within 3 months after the second incomplete resection of the tumor. Therefore, the selection of the timing and options of the procedure after the tumor progressed again worth further exploration. Adequate preoperative assessment in deciding whether to perform the surgery plays an important role.

Previous studies about the rechallenge of sunitinib have preliminarily explored the best individualized treatment for mRCC.[3,4] In this case, sunitinib was initially treated with the standard 4/2 schedule and led to serious AEs. The patient showed well tolerance after adjustment to the 2/1 schedule while the efficacy was ensured. In the presence of disease progression, the patient received a potential and viable novel strategy for sunitinib in mRCC. The tumor was controlled again after sunitinib was rechallenged and at the same time with increased dosage, which indicated that it is feasible to choose individualized treatment for specific patients.[22]

In general, sunitinib is still one of the main treatment strategies for mRCC. While sunitinib rechallenge with increased dosage may stop or reverse the accelerated tumor progression induced by treatment cessation. The combination of sunitinib and personalized management strategies deserves consideration. However, further studies are still needed to validate this conclusion and provide more references for detailed strategies of individualized treatment.

Author contributions

Conceptualization: Hao Zeng.
Data curation: Xingming Zhang, Pengfei Shen, Jin Yao, Ni Chen, Jiyan Liu, Hao Zeng.
Formal analysis: Xingming Zhang, Pengfei Shen, Jin Yao, Ni Chen, Hao Zeng.
Funding acquisition: Pengfei Shen, Hao Zeng.
Investigation: Xingming Zhang, Pengfei Shen, Jin Yao, Ni Chen, Jiyan Liu.
Methodology: Xingming Zhang, Jiyan Liu, Hao Zeng.
Project administration: Pengfei Shen, Hao Zeng.
Resources: Pengfei Shen, Jin Yao, Ni Chen, Jiyan Liu, Hao Zeng.
Software: Xingming Zhang.
Supervision: Hao Zeng.
Validation: Hao Zeng.
Visualization: Hao Zeng.
Writing – original draft: Xingming Zhang.
Writing – review & editing: Pengfei Shen, Ni Chen, Hao Zeng.

References

[1] Kalra S, Rini BI, Jonasch E. Alternate sunitinib schedules in patients withmetastatic renal cell carcinoma. Ann Oncol 2015;26:1300–4.
[2] Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial oftemsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32:760–7.
[3] Zama IN, Hutson TE, Elson P, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer 2010;116:5400–6.
[4] Guevremont C, Mija FI, Isbarn H, et al. Dose escalation of second-line sunitinib results in rapid partial remission of multiple hepatic metastases. Can Urol Assoc J 2009;3:E92–3.
[5] Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–34.
[6] Albiges L, Oudard S, Negrier S, et al. Complete remission with tyrosine kinase inhibitors in renal cell carcinoma. J Clin Oncol 2012;30:482–7.
[7] Johannsen M, Flörcken A, Bex A, et al. Can tyrosine kinase inhibitors be discontinued in patients with metastatic renal cell carcinoma and a complete response to treatment? A multicentre, retrospective analysis. Eur Urol 2009;55:1430–8.
[8] Johannsen M, Staehler M, Ohlmann CH, et al. Outcome of treatment discontinuation in patients with metastatic renal cell carcinoma and no evidence of disease following targeted therapy with or without metastasectomy. Ann Oncol 2011;22:657–63.
[9] Sadeghi S, Albiges L, Wood LS, et al. Cessation of vascular endothelial growth factor-targeted therapy in patients with metastatic renal cell carcinoma: feasibility and clinical outcome. Cancer 2012;118:3277–82.
[10] Powles T, Kayani I, Sharpe K, et al. A prospective evaluation of VEGF-targeted treatment cessation in metastatic clear cell renal cancer. Ann Oncol 2013;24:2098–103.
[11] Koo DH, Park I, Ahn JH, et al. Long-term outcomes of tyrosine kinase inhibitor discontinuation in patients with metastatic renal cell carcinoma. Cancer Chemother Pharmacol 2016;77:339–47.
[12] Abdel-Rahman O, Fouad M. Efficacy and toxicity of sunitinib for non clear cell renal cell carcinoma (RCC): a systematic review of the literature. Crit Rev Oncol Hematol 2015;94:238–50.
[13] Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol 2016;17:378–88.
[14] Calvo E, Grünwald V, Bellmunt J. Controversies in renal cell carcinoma: treatment choice after progression on vascular endothelial growth factor-targeted therapy. Eur J Cancer 2014;50:1321–9.
[15] Porta C, Paglino C, Grunwald V. Sunitinib re-challenge in advanced renal-cell carcinoma. Br J Cancer 2014;111:1047–53.
[16] Adelaiye R, Ciamporcero E, Miles KM, et al. Sunitinib dose escalation overcomes transient resistance in clear cell renal cell carcinoma and is associated with epigenetic modifications. Mol Cancer Ther 2015;14:513–22.
[17] Rini BI, Michaelson MD, Rosenberg JE, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. J Clin Oncol 2008;26:3743–8.
[18] Rini BI, Atkins MB. Resistance to targeted therapy in renal-cell carcinoma. Lancet Oncol 2009;10:992–1000.
[19] Eichelberg C, Vervenne WL, De Santis M, 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;68:837–47.
[20] Amato R, Zhai J, Willis J, et al. A phase II trial of intrapatient dose-escalated sorafenib in patients with metastatic renal cell carcinoma. Clin Genitourin Cancer 2012;10:153–8.
[21] Alt AL, Boorjian SA, Lohse CM, et al. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer 2011;117:2873–82.
[22] Atkinson BJ, Kalra S, Wang X, et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. J Urol 2014;191:611–8.