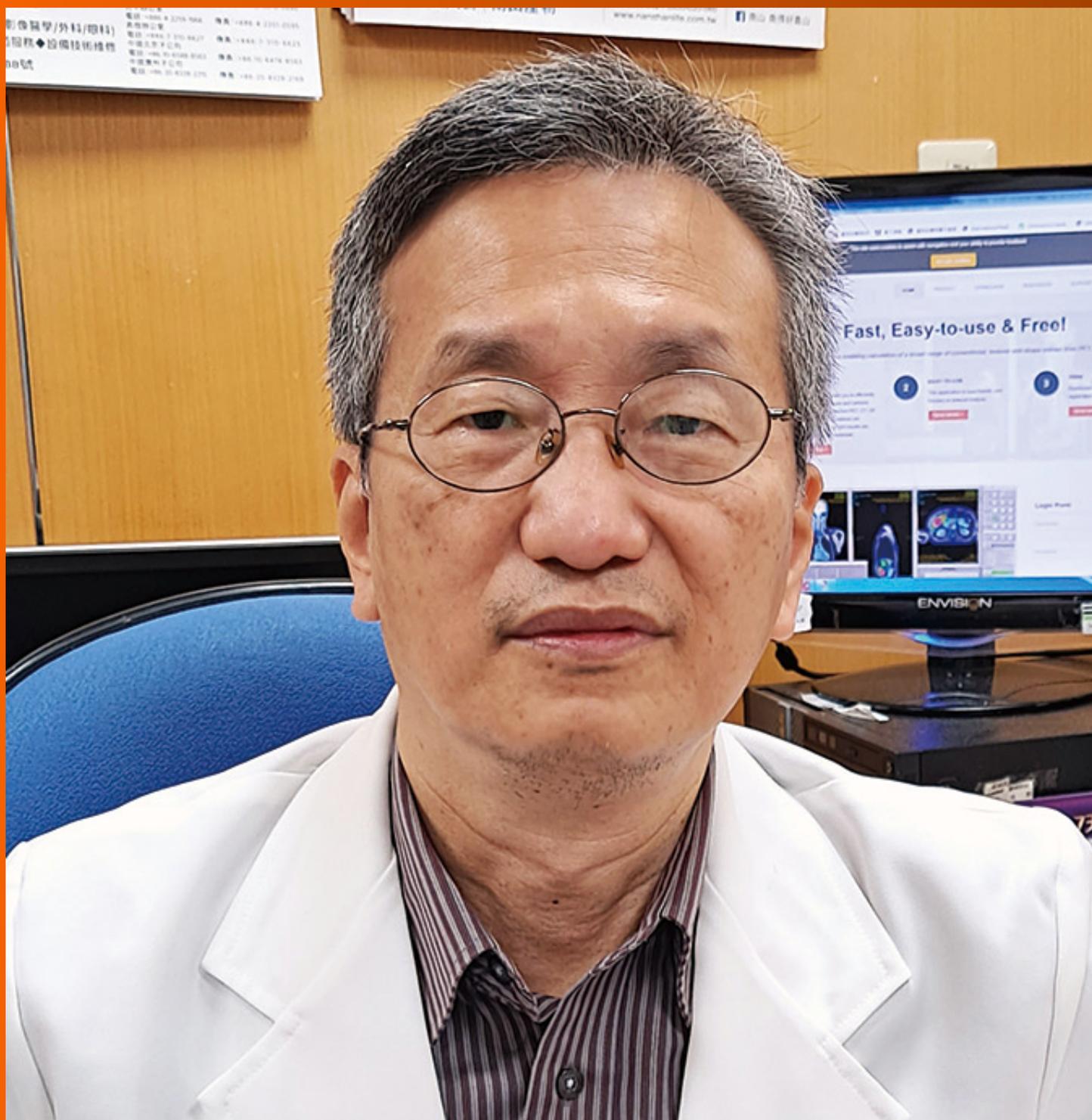


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Successful apatinib treatment for advanced clear cell renal carcinoma as a first-line palliative treatment: A case report

Hang-Ping Wei, Jie Mao, Zu-Liang Hu

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Abstract

BACKGROUND

Apatinib is an orally bioavailable small-molecule receptor tyrosine kinase inhibitor. In December 2014, the China Food and Drug Administration made it the first anti-angiogenic therapy to be approved for treating metastatic gastric cancer. It was specifically designated as a third-line or later treatment for metastatic gastric cancer.

CASE SUMMARY

Here, we present a case of advanced renal cell carcinoma (RCC) with multiple metastases (Stage IV) in a 48-year-old male with an extremely poor general status (Karnofsky 30%). He was initially given pazopanib as a targeted therapeutic. However, he experienced severe adverse reactions within two weeks, including grade IV oral mucositis. We, thus, tried switching his targeted treatment to an apatinib dose of 250 mg once daily since April 2018. The patient demonstrated striking benefits from this switch to the apatinib palliative treatment. Nearly one month later, his pain and other associated symptoms were alleviated. The patient was able to move freely and had an excellent general status (Karnofsky 90%). His progress has been followed up with regularly, allowing for a documented progression-free survival interval of approximately 32 mo.

CONCLUSION

This case suggests that, like other multi-target drugs, apatinib may be a useful first-line therapeutic drug for advanced RCC. It may be a particularly helpful curative option when patients are found to be intolerant of other targeted drugs.

Key Words: Apatinib; Renal cell carcinoma; Targeted therapy; Palliative treatment; Case report

Core Tip: Apatinib, an orally bioavailable small-molecule receptor tyrosine kinase inhibitor, is typically used in the treatment of partial solid tumours. Here, we report a case of advanced renal cell carcinoma (RCC) with multiple metastases (Stage IV) in a 48-year-old man with an extremely poor general status (Karnofsky 30%). Due to his intolerance to pazopanib (patient developed oral mucositis), we attempted targeted treatment with apatinib, at a dose of 250 mg once daily (from April 2018). This led to an excellent recovery response, realising an approximately 32 mo progression-free survival. This case suggests that apatinib, like other multi-target drugs, may be used as a first-line therapeutic treatment for advanced RCC.

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INTRODUCTION

Renal cell carcinoma (RCC) derives from malignant tumours originating in the renal parenchymal urotubular epithelium. Although it only accounts for approximately 2% of all malignant tumours, its morbidity and mortality rates are increasing annually[1,2]. Clear cell RCC (ccRCC) is the most common subtype of RCC, accounting for 80% of all cases[3]. Although surgical excision can cure localised RCC, recurrence is common. In addition, many RCC patients do not present clinical symptoms until they have developed unresectable, locally progressive, or metastatic lesions. Consequently, many patients miss the window for surgery. Moreover, RCC is unresponsive to standard radiotherapy and chemotherapy, and its incidence and mortality rates are increasing with each passing year. Thus, targeted therapy is the most effective treatment for ccRCC patients. Currently, the main targeted drugs for ccRCC include sorafenib, sunitinib, pazopanib, and cabozantinib; all of which achieve anti-tumour effects by impacting vascular endothelial growth factor receptor (VEGFR) expression and inhibiting blood pressure angiogenesis and cell proliferation[2,4].

Apatinib (Hengrui Pharmaceutical Co, Ltd, Shanghai, China) is a highly selective inhibitor of VEGFR-2 tyrosine kinase. In December 2014, it became the first China Food and Drug Administration approved anti-angiogenic therapy for treating metastatic gastric cancer. Its official approved use was as a third-line or later treatment[5]. It acts to specifically inhibit the VEGFR tyrosine kinase activity, thereby inhibiting tumour angiogenesis. Since its approval, given its effectiveness in treating gastric cancer, it has also been used to treat other tumours. Hence, apatinib has shown to be a strikingly effective new option against multifarious malignancies, including advanced non-small cell lung cancer, metastatic triple-negative breast cancer, angiosarcoma, desmoplastic small round cell tumour, advanced intrahepatic cholangiocarcinoma, and myxoid/round cell liposarcoma[6-10].

However, to the best of our knowledge, cases have yet to be reported regarding apatinib's usefulness in both the treatment of RCC and controlling tumour growth. Thus, in the current report, we present an advanced ccRCC case with multiple metastases (Stage IV) in a 48-year-old male with an extremely poor general status (Karnofsky 30%).

CASE PRESENTATION

Chief complaints

In March 2010, a middle-aged (48-year-old) man was admitted to Dongyang Hospital Affiliated to Wenzhou Medical University complaining of soreness and swelling on his waist and back.

History of present illness

The patient's symptoms of persistent pain had started one year prior. However, two weeks before admission, it had worsened to the point that he could not lie down on his back at night. Oral analgesics did not control his pain, which he reported suffering from in frequent bouts.

History of past illness

In May 2017, the patient was admitted to the Fourth Affiliated Hospital of Zhejiang University's Medical College. Urinary system and bladder ultrasounds showed the presence of a parenchymal space-occupying tumour of the left kidney. Chest and abdomen computed tomography (CT) scans suggested

that the tumour had triggered implantation metastasis at multiple sites, including parapyloric nodules, lumbar areas, multiple nodules in both lungs, left pleura, left breast, and the abdominal wall. Realising the seriousness of his condition, the patient immediately visited the Cancer Hospital affiliated with Fudan University, where he was advised to undergo a left nephrectomy, followed by adjuvant therapy. However, the patient was resistant and refused the suggested treatment. Instead, he consumed traditional Chinese medicine orally at home. Unfortunately, by March 2018, the tumours had progressed and the mass on his back had grown more.

Personal and family history

The patient had no history of smoking or drinking alcohol. There was no relevant family history.

Physical examination

The patient's vital signs were stable in March 2018. However, the clinical examination showed tenderness in the lower back and localised skin swelling.

Laboratory examinations

Blood tests showed increased leukocytes and tumour markers. The neutrophil, hemoglobin, platelets and biochemistry was normal.

Imaging examinations

Lumbar CT scans, taken on March 5, 2018, showed that the patient's lumbar spinous process level space had been blocked by the deterioration and absorption of lumbar 2 appendages and the invasion of the spinal canal (Figure 1).

Further diagnostic work-up

Considering the medical history and follow-up treatments in this case, a puncture biopsy of the mass was recommended. Thus, on March 17, 2018, a puncture biopsy was performed on the back tumour, with guided colour Doppler ultrasound. The observed malignant tumours were consistent with ccRCC according to their morphology and histology; CK+, CK7-, CK20-, cam5.2+, CD10+, EMA+, 34beta E12-, Ki-67+ (10%) (Figure 2).

MULTIDISCIPLINARY EXPERT CONSULTATION

This patient had a clear diagnosis of ccRCC with multiple metastases (Stage IV; IMDC mid-risk). Given the multiple metastases, surgery was not advisable. Instead, medical treatment was considered.

FINAL DIAGNOSIS

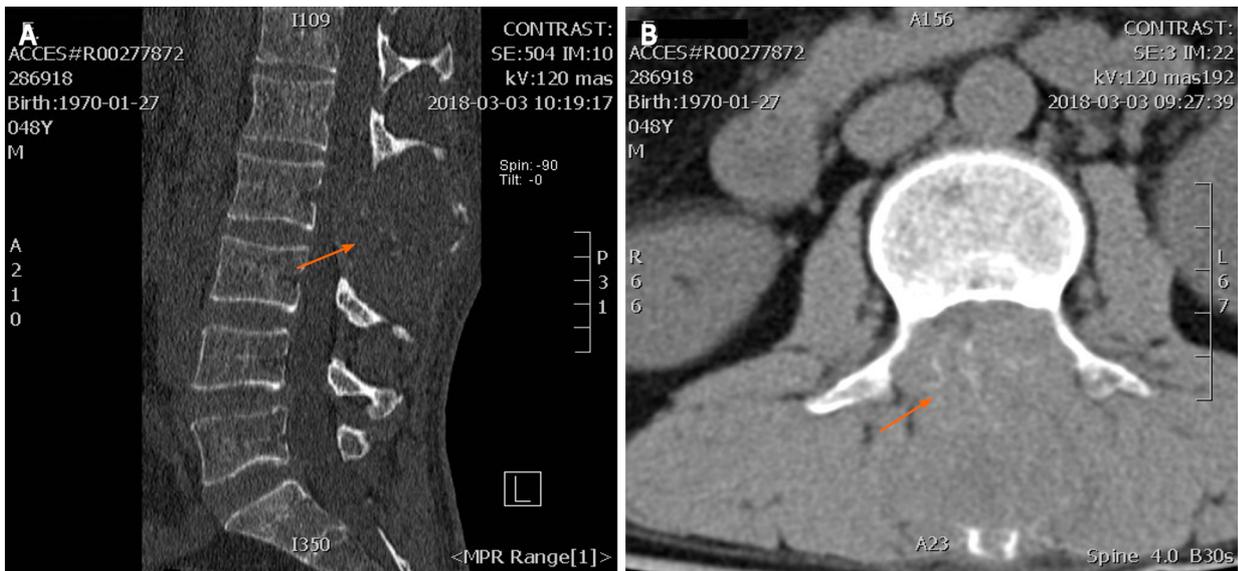
The patient was diagnosed with ccRCC with multiple metastases (Stage IV; IMDC mid-risk) in various organs, including the lungs (contralateral), bones, pleura, abdominal cavities, and lymph nodes. The patient had an extremely poor general status (Karnofsky 30%) and was informed on his poor prognosis.

TREATMENT

Initially, the patient was administered pazopanib targeted treatment. However, two weeks later he experienced severe adverse reactions in the form of grade IV oral mucositis. Considering his intolerance to pazopanib, we attempted targeted treatment with apatinib, at a dose of 250 mg daily since April 2018. There were no grade III or higher adverse reactions during apatinib treatment.

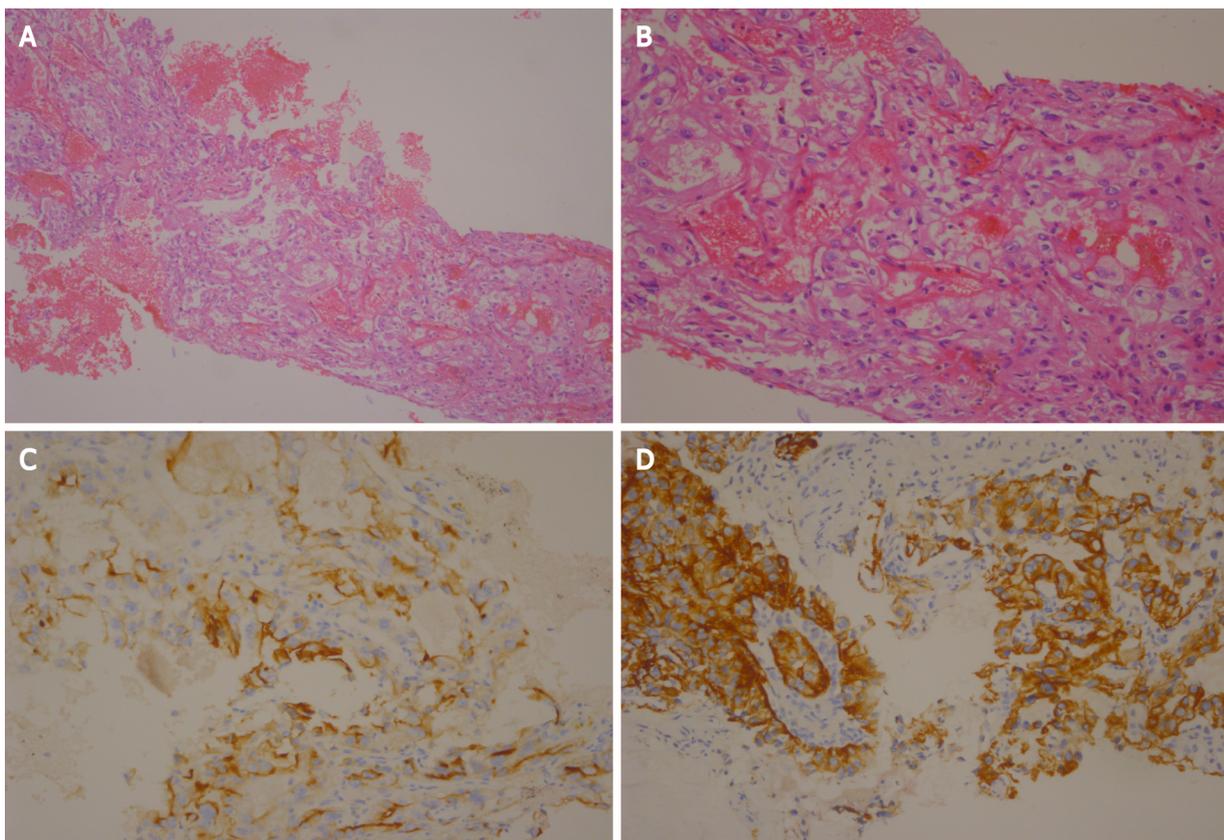
OUTCOME AND FOLLOW-UP

In response to apatinib treatment, the lump in his back shrank after one week. The patient was thus able to lie down, and his pain in so doing was alleviated. He was able to move freely and his performance status improved drastically (Karnofsky 90%). CT taken on July 26, 2018, revealed left inferior pole RCC (diameter: 4.5 cm), L2 spinous process metastatic bone tumours secondary to corresponding plane spinal stenosis, and multiple metastatic tumours in both the lungs (both the length and diameter of the lesion were approximately 1.0 cm), and he had a stable disease (SD), according to the RECIST 1.1 criteria (Figure 3). After several months, a follow-up CT taken on October 20, 2018, and compared with the prior scan (July 26, 2018), suggested that the left inferior pole RCC had reduced in size (diameter: 3.9 cm).



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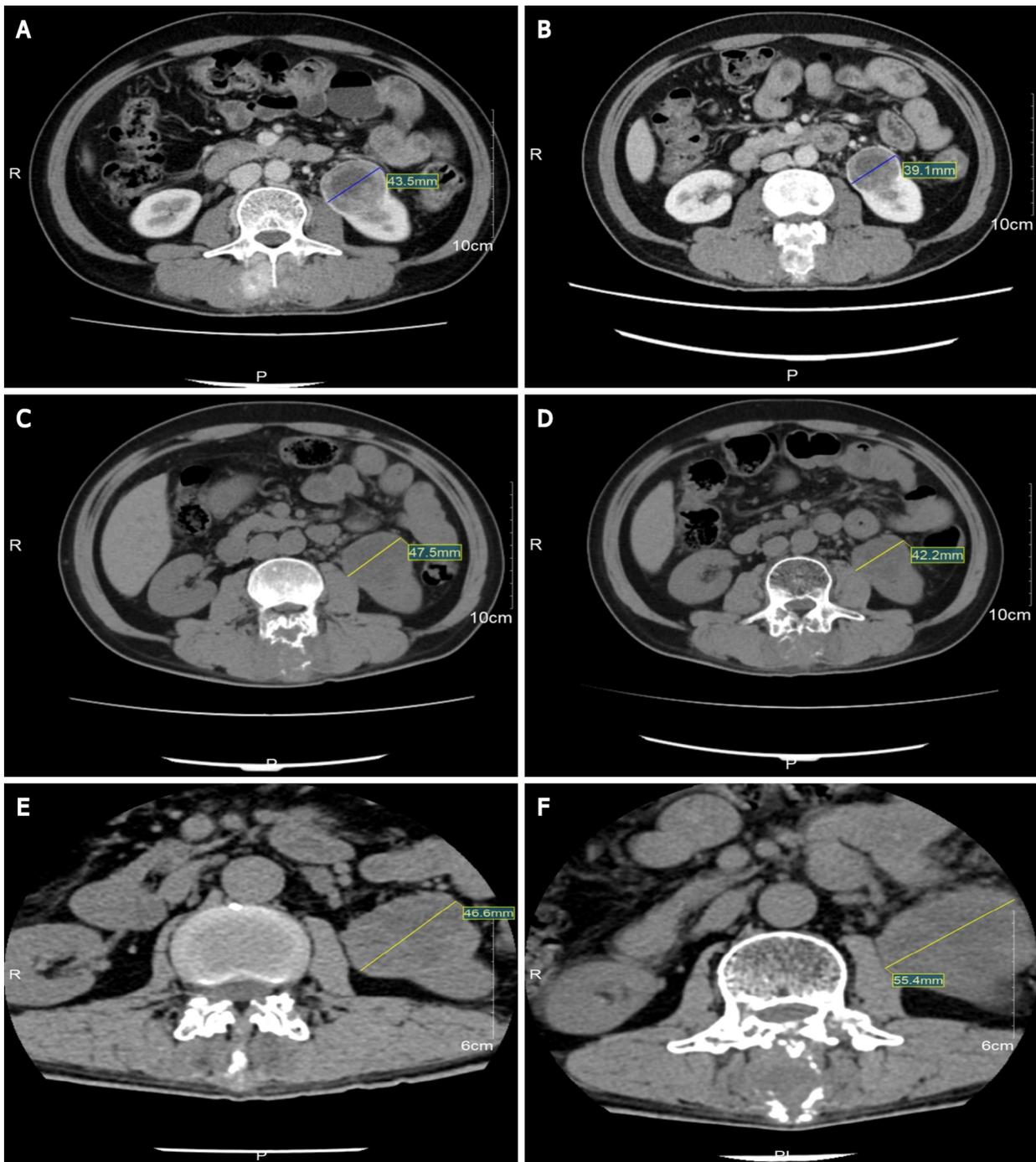
Figure 1 Lumbar computed tomography was taken on March 5, 2018, which showed lumbar spinous process level occupied space with destruction and absorption of lumbar 2 appendages and invasion of the spinal canal. A: Sagittal sections of the masses; B: Coronal sections of the masses (red arrow).



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Figure 2 Haematoxylin and eosin staining of a tumour section. A: Under × 10 times microscope; B: Under × 40 times microscope. Immunohistochemical staining of a tumour section; C: It showed that CD10 was positive; D: It showed that CD20 was negative.

Moreover, the rest of the metastatic tumours did not demonstrate any noticeable change (in terms of growth) (Figure 3). Furthermore, the patient showed a SD, according to the RECIST 1.1 criteria. The follow-up CT taken on March 5, 2019 showed that the left inferior pole RCC had enlarged (diameter: Approximately 4.7 cm). However, the progression was slow, according to the RECIST 1.1 criteria



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Figure 3 Computed tomography images during treatment showing the changes of the mass. A: Computed tomography (CT) images obtained on July 26, 2018; B: CT images obtained on October 20, 2018; C: CT images obtained on March 5, 2019; D: CT images obtained on December 24, 2019; E: CT images obtained on October 5, 2020; F: CT images obtained on December 14, 2020.

(Figure 3). During this period, combination immunotherapy was recommended due to the increase in tumour size. However, the patient rejected it for economic reasons. Thereafter, he was followed up with several times and was reported to be stable till December 2020. The follow-up CT, taken on December 14, 2020, showed that the left inferior pole RCC had increased in size (diameter: Approximately 5.5 cm). Considered together with the other lesions, this indicated that the disease had resumed progression (Figure 3). Strikingly, until this point, the patient had experienced 32 mo of progression-free survival (PFS).

DISCUSSION

RCC is considered a serious disease worldwide because of the extent to which it endangers human life and health. It demonstrates insidious onset, low survival rate, and high morbidity and mortality. RCC is the second most common urinary tumour, accounting for 2%–3% of all adult malignant tumours[2]. Currently, the best treatment for RCC is surgical resection. In 2010, radical nephrectomy was proposed as a viable option for advanced RCC patients in sufficiently good general condition such that they could tolerate surgery[11]. However, approximately one third of RCC patients demonstrate distant metastasis at the time of initial diagnosis. Thus, they have missed the window for surgery. Statistically, RCC patients showing a 2-year survival rate amount to less than 20% of all cases, whereas the 5-year survival rate is approximately 10% [2]. Therefore, pursuit of medical treatment for RCC is also extremely important. Luckily, over the past decade, a range of therapeutic options have been approved for mRCC, including the targeted, immune checkpoint, and combined immune checkpoint treatments[12]. In the mid to late 2000s, targeted therapies, including inhibitors of VEGF and the mammalian target of rapamycin pathway have entered into the clinical toolkit, thus expanding the range of standard ccRCC therapy options[13]. Consequently, the 5-year survival rate for advanced RCC has increased to nearly 20% [2]. Recent studies have shown that immunotherapy and target therapy combined with immunotherapy have led to positive results in the PFS of advanced RCC patients[14,15].

Researchers have shown that targeted therapies, such as bevacizumab, sunitinib, and axitinib, have a 25%–35% overall response rate among treatment-naive patients, a disease control rate of 45%–80%, and a median PFS ranging from 6.5–11 mo[16]. Currently, immunotherapy has also been used as a first-line treatment[17]. The median PFS for advanced first-line RCC immunotherapy is between 11.2 and 15.1 mo [18–20]. However, immunotherapy, being very expensive and not yet insured, is not an economic first-line RCC treatment[21].

Apatinib is an orally bioavailable small-molecule VEGFR2 tyrosine kinase inhibitor. It inhibits VEGF-mediated endothelial cell migration and proliferation, thereby arresting angiogenesis in tumours[22]. In addition, this agent mildly inhibits c-Kit and c-Src tyrosine kinases. Studies have shown that apatinib can arrest the growth of tumour cells in advanced gastric cancer patients. It has been shown to similarly affect advanced epithelial ovarian cancer, recurrent malignant glioma, and metastatic breast cancer[5,6,8,23,24].

In the present case, the patient was diagnosed with ccRCC with multiple metastases (Stage IV) and was in deplorable physical condition. Therefore, targeted therapy was recommended. Given the patient's intolerance to pazopanib and our uncertainty with regards to his response to sunitinib, we chose apatinib as this drug had been reported to be successful in treating various malignancies. The patient showed a positive clinical response to apatinib. His general status improved drastically, and nearly 32 mo of PFS was realised, which was longer than any previously reported case. Although, the patient showed a slow disease progression, apatinib was still effective in reversing disease severity. Thus, we posit an ideal treatment combination of apatinib and immunotherapy. Unfortunately, the patient did not receive immunotherapy concurrently for financial reasons.

However, this study has some limitations. Because case reports cannot replace randomised controlled trials, it is unclear whether apatinib is suitable for all RCC patients. Further prospective studies are required to optimise the use of apatinib in the treatment of RCC and identify patients that can benefit from this agent.

CONCLUSION

In conclusion, this case report indicates that apatinib significantly augmented the quality of life for an RCC patient. It also markedly improved his PFS. Thus, apatinib, like other multi-target drugs, may be useful as a first-line therapeutic drug for advanced RCC. It may be a particularly helpful curative option when patients are found to be intolerant of other targeted drugs.

FOOTNOTES

Author contributions: Hu ZL and Wei HP were medical oncologist of the patients, who consulted the literature and participated in the drafting of the manuscript; Mao J was responsible for the imaging data of patients; all authors have approved the final version of the manuscript to be submitted.

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