CASE REPORT

Continuous remission of renal cell carcinoma with tumour thrombus after severe adverse events following short-term treatment with sunitinib

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SUMMARY

A 64-year-old Japanese man with renal cell carcinoma (RCC) and tumour thrombus in the inferior vena cava was treated with sunitinib. Two weeks after treatment, he was hospitalised for disturbance of consciousness. Laboratory tests revealed high-grade hypoglycaemia, hyponatraemia, liver dysfunction and thrombocytopenia with disseminated intravascular coagulation. Sunitinib was discontinued and the patient recovered after a protracted platelet transfusion. At 5 months after treatment, CT revealed that the tumour thrombus had disappeared and other lesions had regressed. MRI at 15 months revealed further regression and suggested the possibility of histological remission according to the signal intensity of fibrosis. A partial response persisted at 20 months after treatment, despite residual accumulation in the renal tumour evident on positron emission tomography. In summary, we present a case of locally advanced RCC accompanied by severe adverse events that showed a significant and durable response to treatment with sunitinib for just 2 weeks.

BACKGROUND

Sunitinib, a multitargeted tyrosine kinase inhibitor (TKI), is a standard treatment for patients with advanced renal cell carcinoma (RCC). Sunitinib acts as an inhibitor of the vascular endothelial growth factor receptor, platelet-derived growth factor and other tyrosine kinases. Sunitinib can cause serious adverse events, some of which are considered to be associated with its antitumour effects.¹ Here, we present a case of advanced RCC treated with short-term sunitinib, in which significant remission was achieved after severe adverse events.

CASE PRESENTATION

The patient was a 64-year-old Japanese man with a history of diabetes, hypertension and chronic kidney disease (CKD). He was referred to our hospital for progression of CKD over the course of a few months. CT and MRI revealed a bladder tumour, left renal tumour with renal hilar lymph node involvement and tumour thrombus in the inferior vena cava (IVC) up to the right atrium. Blood tests discovered anaemia, increased serum creatinine, mild hyponatraemia and mild liver dysfunction. A biopsy of the left renal tumour and transurethral resection of the bladder tumour identified them as a Fuhrman grade 2 clear cell carcinoma and inverted papilloma, respectively.

Sunitinib administration was started at a dose of 37.5 mg daily for 2 weeks followed by 1 week off. One day after the 2 weeks of treatment, the patient was emergently hospitalised for disturbance of consciousness. Laboratory tests revealed hypoglycaemia (Common Terminology Criteria for Adverse Events grade 4), hyponatraemia (grade 4), liver dysfunction (alanine aminotransferase and aspartate aminotransferase grade 4 and bilirubin grade 3) and thrombocytopenia (grade 3 on admission and grade 4 thereafter) with disseminated intravascular coagulation (DIC) (grade 2). The results of a hormonal examination that included antidiuretic hormone and adrenal hormone were almost normal. CT showed that the IVC was slightly swollen and the left renal tumour was unchanged. Sunitinib treatment was discontinued. After correction of serum glucose and sodium, the patient recovered consciousness. DIC was prolonged and treated with a platelet transfusion. Viral hepatitis was excluded and liver function gradually improved. Renal function returned to previous levels and serum sodium normalised (figure 1). CT imaging at 5 months after sunitinib treatment showed that the tumour thrombus in the IVC was indistinct, and that the left renal tumour and some of the involved lymph nodes had regressed, which is a partial response according to V.1.1 of the Response Evaluation Criteria in Solid Tumours. Subsequently, the left renal tumour and all lymph nodes gradually decreased in size. MRI at 15 months after sunitinib treatment revealed that the IVC and left renal vein were obstructed and replaced by fibrotic tissue with the same signal intensity in the left renal tumour, suggestive of a histological response (figure 2). Positron emission tomography (PET) and CT at 20 months after sunitinib treatment showed a slight regression and residual accumulation in part of the renal tumour. Although PET and CT findings suggested the presence of a viable residue of the renal tumour, our patient did not desire further consolidation therapy because of his comorbidities and performance status.

DISCUSSION

Regression of RCC after TKI treatment is frequently observed within a few months. Albiges *et al* reported 36 cases of patients with metastatic RCC who experienced complete response (CR) following treatment with sorafenib or sunitinib. CR was achieved in a median time of 12.6 months (range 2–28 months) after the start of TKI therapy.² Tsuzuki *et*

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Figure 1 Clinical course and change of laboratory findings. Each arrow represents the thrombocyte transfusion of 10 units. ALT, alanine transaminase; AST, aspartate transaminase.

al reported histopathological changes in clear cell RCC after TKI. They indicated that vasculopathy of tumour vessels in or adjacent to the necrotic or degenerative areas were observed in tumour after TKI regardless of treatment period.³ In this case, the tumour regressed and demonstrated durable remission after sunitinib treatment for just 2 weeks. To our knowledge, this is the shortest duration of sunitinib treatment to achieve a significant and durable response.

Our patient exhibited liver dysfunction and thrombocytopaenia with DIC after sunitinib treatment. In a global expanded-access trial of sunitinib for metastatic RCC, thrombocytopaenia was observed in 26% of patients (10% at grades 3/4) and alanine aminotransferase was increased in 3% of patients (1% at grades 3/4).⁴ The frequency of DIC after sunitinib was even lower. In this case, DIC may have been triggered by liver dysfunction and thrombocytopaenia. Recently, thrombocytopaenia was designated one of the on-target adverse events of sunitinib.¹ As this case was modified by DIC, thrombocytopaenia may have forecast the degree of effectiveness of the treatment.

Figure 2 MRI T2WI before and after sunitinib treatment. Arrows show renal tumour, renal hilar lymph node and tumour thrombus in the IVC, and each of them regressed after 15 months. IVC, inferior vena cava; T2WI, T2-weighted image.

Miura *et al* described a patient with metastatic RCC who exhibited grade 4 thrombocytopaenia and a 30% reduction in lesions after sunitinib treatment for 10 days.⁵ In that case, the blood concentration of sunitinib was much higher than usual. Mizuno *et al* stated that the blood concentration of sunitinib is associated with polymorphism of the ATP binding cassette subfamily G member 2 (ABCG2) 421C>A.⁶ This genetic variant is significantly related to severe thrombocytopaenia following sunitinib treatment and is more frequently observed in Asian populations, including Japanese individuals, compared with in non-Asians.⁷ In this case, the severe adverse events and dramatic effect of treatment may be attributable to genetic susceptibility to TKI and overexposure to sunitinib, although the blood concentration of sunitinib was not confirmed. In future, genetic evaluation and management of the trough level of drugs may facilitate appropriate dose setting to achieve the best outcome with tolerable adverse events. The liver dysfunction evident in this case may have been caused by an adverse reaction to sunitinib and the liver congestion due to tumour thrombus. This case fulfilled the general criteria of drug-induced liver injury except for the lack of eosinophilia or atypical lymphocytosis, which are typical laboratory findings.⁸ Reportedly, 7%–31% of patients with RCC and tumour thrombus in the IVC present with symptoms of IVC syndrome such as foot oedema, dilatation of superficial veins, varicocele, proteinuria and liver dysfunction.⁹ In this case, the renal and liver dysfunction evident at presentation may have been a manifestation of tumour thrombus. Sunitinib treatment may have accelerated liver congestion (Budd-Chiari syndrome) by transient swelling of the tumour thrombus during a necrotic change.

Currently, there is no consensus on the appropriate adjuvant therapy after remission. Albiges *et al* reported that the recurrence rate in patients with TKI-induced CR was 33% or 44% with or without adjuvant TKI at a median time of 7.9 months (range 3–32 months) with a median follow-up duration of 8.5 months after the cessation of TKI therapy.² Although we also proposed secondary treatment with other TKIs, mammalian target of rapamycin inhibitors or interferon alpha, our patient did not desire further consolidation therapy including partial nephrectomy because of his comorbidities and performance status. Therefore, close monitoring was necessary thereafter.

Learning points

- We present a case of locally advanced renal cell carcinoma accompanied by severe adverse events that showed a significant and durable response to treatment with sunitinib for just 2 weeks.
- The severe adverse events and dramatic effect of treatment may be attributable to genetic susceptibility to tyrosine kinase inhibitor and overexposure to sunitinib
- Genetic evaluation and management of the trough level of drugs may facilitate appropriate dose setting to achieve the best outcome with tolerable adverse events.

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Competing interests None declared.

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