CASE REPORT

Lethal acute liver failure in a patient treated with sunitinib

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SUMMARY

Sunitinib is a tyrosine kinase inhibitor that is used as an anticancer drug in renal cell carcinoma (RCC), pancreatic neuroendocrine tumours (PNETs) and gastrointestinal stromal tumour. Elevated liver enzymes are frequently observed during treatment but acute liver failure is uncommon. We describe a case of fulminant acute liver failure and acute kidney injury during treatment with sunitinib for metastatic RCC.

BACKGROUND

Sunitinib is a tyrosine kinase inhibitor with antitumour and antiangiogenic activity. The drug targets platelet-derived growth factor, vascular endothelial growth factor, stem cell growth factor (c-KIT) and FLT3 receptor kinases. Sunitinib is a major substrate for hepatic cytochrome CYP3A4 and is excreted into faeces (70–84%) and urine (16%). Common adverse effects are bone marrow depression, fatigue, stomatitis, abdominal discomfort, diarrhoea, skin rash, hand-foot syndrome, hypertension and hypothyroidism. Although elevated liver enzymes and increased serum creatinine frequently occur during treatment with sunitinib, overt hepatic or renal failure is exceedingly rare.

CASE PRESENTATION

A 79-year-old Caucasian man was admitted to our hospital with acute-onset jaundice during the eight cycle of sunitinib treatment for metastatic renal cell carcinoma (RCC). His condition had suddenly deteriorated 1 week before admission, with progressive fatigue and malaise.

One year earlier, he had presented with RCC as a coincidental finding during hospital admission for severe diverticulitis. His medical history was otherwise unremarkable except for paroxysmal atrioventricular nodal re-entry tachycardia, for which he used metoprolol 50 mg daily. CT scan revealed a large mass in the right kidney, with three metastatic lesions in the right lung. He underwent an uncomplicated sigmoid resection and nephrectomy. Pathological examination revealed a 9 cm large Fuhrman grade 3 clear cell RCC with extension into the perinephric fat and renal vein; the sigmoid showed inflammation without malignancy. After recovery from surgery, CT scan showed progression of the pulmonary metastases and a new (probably metastatic) liver lesion. Therefore, the patient was started on treatment with sunitinib 50 mg/day (for 4 weeks followed by 2 weeks off treatment). After five cycles, the dose was reduced to 37.5 mg/day because of adverse effects (mainly fatigue,

stomatitis and diarrhoea). Further treatment with sunitinib was uneventful (including normal serum liver enzymes and bilirubin at each treatment cycle), and evaluation CT scan performed <10 days before hospital admission for acute-onset malaise and jaundice showed ongoing slight decrease of the pulmonary metastases and disappearance of the liver lesion, and was otherwise unremarkable including normal findings of liver and left kidney.

On admission, we saw an ill-appearing icteric man with a pulse rate of 82 bpm, blood pressure 165/101 mm Hg, oxygen saturation 100% and body temperature 35.5°C. Physical examination was otherwise normal. Laboratory assessment revealed striking abnormalities including acute liver and kidney failure, metabolic acidosis and disseminated intravascular coagulation (table 1).

Ultrasonography showed normal aspect of the abdominal organs with normal liver blood flow. Chest X-ray showed the known metastatic lesions but no infiltrates and no signs of cardiac decompensation. ECG showed a right bundle block without signs of ischaemia. Multiple blood and urine cultures were negative. Acute viral hepatitis was excluded with serological studies for hepatitis A, B, C and E, along with cytomegalovirus and Epstein-Barr virus. Our patient had used no medications (including complementary/alternative products) other than metoprolol and sunitinib, which he had discontinued shortly before admission. Nonetheless, the patient's condition deteriorated rapidly, and 4 days after admission, he died in a hepatic coma. Permission for autopsy was not obtained.

DISCUSSION

We present a case of lethal acute liver failure in a patient treated with sunitinib for RCC. During treatment, liver enzymes were monitored frequently and showed no abnormalities throughout the first seven 6-week cycles of treatment. Recent CT scan and actual ultrasonography showed a normal aspect of the liver, with signs of neither venous occlusion nor biliary obstruction. Bacterial infection was very unlikely as the cause of this patient's fulminant liver failure, and acute viral hepatitis was excluded with serological tests. In this case, no explanation for acute liver failure was found other than the use of sunitinib.

Fulminant liver failure associated with treatment using sunitinib is rare and the underlying mechanism is unclear. We suggest that the fulminant liver failure in this case was a type B adverse drug reaction to sunitinib. In contrast to type A, type B reactions are idiosyncratic, unpredictable, usually

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Table 1 Laboratory values in the patient

	28 Days before admission	Day 1	Day 2	Day 3	Normal ranges
Haemoglobin	6.2	8.0		7.0	(7.5–10.0 mmol/L)
Leucocytes	3.8	7.4	9.1	9.1	(4.3–10.0×10 ⁹ /L)
Platelets	145	20	29	25	(150–400×10 ⁹ /L)
Prothrombin time		28	58	54	(8–11 s)
APTT		34	50	50	(20–30 s)
Fibrinogen		0.9	0.5	0.5	(2.0–4.5 g/L)
D-Dimer		>3200	>3200		
Creatinine	118	266	341	378	(55–95 µmol/L)
Total bilirubin	7	92	157	182	(0–17 µmol/L)
Direct bilirubin		55	122	144	(0–17 µmol/L)
ASAT	18	2640	4105	5964	(0–37 IU/L)
ALAT	15	1844	2511	3565	(0–31 IU/L)
LDH	226	3386	5005	6721	(0–450 IU/L)
Alkaline phosphatase	60	78	70	80	(25–120 IU/L)
γ-GT	25	35	47		(0–35 IU/L)
Lactate		8.7	11.6	5.7	(0.5–2.2 mmol/L)

ALAT, alanine aminotransferase; APTT, activated partial thromboplastin time; ASAT, aspartate aminotransferase; LDH, lactate dehydrogenase; γ-GT, γ glutamyltransferase.

uncommon, dose independent and unrelated to the drug's known pharmacology.¹

Using the Naranjo adverse effect probability scale, the relationship between sunitinib and hepatotoxicity in this case can be rated as 'probable' (figure 1).² A higher causality association could not be reached due to the fulminant clinical course (ie, no improvement after drug discontinuation and re-challenge not possible). In general, causality assessment can be complicated by lack of validated assessment systems, incomplete information and difficulty interpreting data.³

Figure 1 Naranjo Adverse Drug Reaction Probability Scale. Scores based on the presented case.

Question	Yes	No	Do Not Know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
TOTAL SCORE:				6

A recent meta-analysis of sunitinib adverse events in metastatic RCC described elevated liver enzymes in 40% of 5658 patients. Grade III/IV elevated liver enzymes occurred in 3% of patients and no fatal hepatotoxicity was reported.⁴ We found four cases of liver failure in patients treated with sunitinib. Mermershtain *et al*⁵ described a patient with acute liver failure during the first cycle of sunitinib for RCC. Another case report mentioned sunitinib-related acute liver failure in a woman with RCC during the fifth treatment cycle, which was reversible after discontinuation of the drug.⁶ The third case described a patient treated with nine cycles of sunitinib for metastatic gastrointestinal stromal tumour, who developed liver failure and died after 4 days.⁷ Finally, a case of fatal liver failure was reported in a patient with ovarian cancer.⁸

In conclusion, we report a case of fulminant acute liver failure associated with sunitinib treatment for metastatic RCC. Other reasonable causes of acute hepatic failure were excluded and the cause–effect relationship was rated as probable according to the Naranjo scale. Although frequent monitoring of liver tests continues to be advisable during treatment with sunitinib, it would not have prevented the lethal acute hepatotoxicity in this patient.

Learning points

- ▶ Elevated serum liver enzymes occur frequently during sunitinib treatment but acute liver failure has rarely been described.
- ▶ Acute liver failure seems to be dose independent and can occur unexpectedly.
- ▶ Clinicians should be aware of liver failure as a complication of treatment with sunitinib, even after multiple cycles of treatment.

Competing interests None declared.

Patient consent Not obtained.

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