Life-Threatening Complications Associated with the Tyrosine Kinase Inhibitor Sunitinib Malate

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Key Words

Sunitinib · Renal cell carcinoma · Heart failure · Kidney failure

Abstract

Adverse events associated with sunitinib, such as cardiac toxicities, renal damage, and hemostatic complications, are well known. The authors report 3 cases in which patients experienced severe life-threatening complications after commencing sunitinib treatment. One patient developed heart failure with dilation of the left ventricle and decrease in the ejection fraction after one cycle of sunitinib and required treatment with an angiotensin-converting enzyme inhibitor, loop diuretics, and dobutamine. Another patient developed coronary artery stenosis after one cycle of sunitinib and was managed through percutaneous coronary intervention. Although follow-on coronary angiography revealed normal findings after 6 further cycles of sunitinib, this patient eventually expired due to multi-organ failure. The third patient had chronic renal failure before sunitinib treatment and required hemodialysis due to acute-on-chronic renal failure after commencing sunitinib treatment.

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Introduction

Sunitinib malate is a novel multi-target receptor tyrosine kinase inhibitor (TKI) with established efficacy in the treatment of metastatic renal cell carcinoma (mRCC) [1, 2]. However, sunitinib is associated with adverse events, which range from mild fatigue and hand-foot syndrome to life-threatening cardiac toxicity [1, 3]. The authors hereby present their experience in 3 cases of life-threatening complications associated with cardiac and renal toxicities after initiation of sunitinib treatment. Patient characteristics are shown in table 1.

Case Reports

Case 1

A 48-year-old female was diagnosed with RCC in the mid- and lower pole of the left kidney. She underwent open radical nephrectomy in November 2003. In 2007, follow-up computed tomography (CT) revealed disease recurrence in the right upper lung and precarinal lymph node. Echocardiography prior to sunitinib initiation showed relaxation abnormality with minimal mitral valve regurgitation (diastolic left ventricular internal diameter [LVIDd] 5.55 cm, systolic left ventricular internal diameter [LVIDs] 4.04 cm, and ejection fraction [EF] 52.4%). After undergoing 1 cycle of sunitinib treatment, the patient developed dyspnea, generalized edema, and pleural effusion. Echocardiogram

Fig. 1. **a** Normal cardiac echocardiogram before receiving sunitinib. **b** Cardiac echocardiogram showing decreased global left ventricle systolic function and wall motion (EF 27.5%) as well as dilated left ventricle (LVIDd 6.01 cm, LVIDs 4.96 cm) 4 weeks after receiving sunitinib.

Table 1. Characteristics of patients

	Surgery	Pathology	Postoperative stage	Sunitinib dosage	Sunitinib medication duration	Complication	Management
Patient 1	open radical nephrectomy	RCC, clear cell type, Fuhrmann nuclear grade 3	T2N0M0	50 mg q.d.	1 cycle	congestive heart failure	angiotensin-converting enzyme inhibitor, loop diuretic, and dobutamine
Patient 2	open radical nephrectomy	RCC, clear cell type, Fuhrmann nuclear grade 3	T3bN0M0	50 mg q.d.	7 cycles	coronary artery stenosis, multi-organ failure	percutaneous coronary intervention
Patient 3	laparoscopic radical nephrectomy	RCC, clear cell type, Fuhrmann nuclear grade 3	T1N0M1	50 mg q.d.	1 cycle	acute kidney failure	hemodialysis

revealed decreased global left ventricle systolic function and wall motion (EF 27.5%), and dilated left ventricle (LVIDd 6.01 cm, LVIDs 4.96 cm) (fig. 1). Sunitinib therapy was stopped and the patient's heart failure was managed with an angiotensin-converting enzyme inhibitor, loop diuretics, and dobutamine. Follow-up echocardiogram 6 months later revealed normal findings (LVIDd 58.09 mm, LVIDs 37.73 mm, EF 63.55%), and the patient is now receiving sorafenib in combination with heart failure medication without further complications.

Case 2

A 53-year-old female was diagnosed with RCC in the lower pole of the right kidney and underwent open radical nephrectomy in April 1994. In August 2007, CT revealed the presence of multiple parenchymal nodules in the right upper lobe and right middle lobe of the lung. Echocardiogram revealed relaxation abnor-

malities with mild mitral valve regurgitation (EF 71.2%). After receiving 4 weeks of sunitinib, the patient developed complications including generalized weakness and dyspnea. Electrocardiogram findings were suggestive of inferior myocardial infarction. Evaluation of the patient with a follow-on echocardiogram revealed decreased EF (50%), and hypokinesia of the basal posterior and inferior walls. Cardiac angio-CT showed the right coronary artery, left anterior descending coronary artery, and left circumflex coronary artery to be stenotic. Percutaneous coronary intervention was subsequently performed on the left anterior descending coronary artery with insertion of two Cypher stents. The patient continued on sunitinib treatment and developed general weakness, dyspnea, and hematochezia after 6 further cycles. The levels of blood urea nitrogen/creatinine (BUN/Cr 170/6.5 mg/dl), liver enzymes (aspartate aminotransferase/alanine aminotransferase [AST/ALT] 775/146 mg/dl), and cardiac enzymes (creatinine kinase

[CK] 54278 u/l, CK-MB 292 ng/ml, myoglobin 3918 ng/ml, troponin-I 0.19 ng/ml) increased abruptly, suggestive of acute myocardial infarction, acute renal failure, toxic hepatitis, and lower gastrointestinal bleeding. Although coronary angiography revealed normal findings, the patient expired one hour after commencing hemodialysis due to multi-organ failure.

Case 3

A 62-year-old male underwent laparoscopic radical nephrectomy for RCC in the lower pole of the left kidney in November 2005. His BUN/Cr level before surgery was 7/1.1 mg/dl, which rose to 20/4.0 mg/dl after surgery. His right renal cortex was almost invisible on ^{99m}Tc dimercaptosuccinic acid scintigram, indicating near nonfunction of the renal cortex. In May, 2008, he was diagnosed with bilateral adrenal metastasis and underwent bilateral adrenalectomy. He was commenced on sunitinib treatment after surgery. His BUN/Cr level before commencing sunitinib treatment was 37/3.2 mg/dl. 15 days later he suffered generalized weakness and azotemia. The results of the follow-up assessment of BUN/Cr level were 127/6.2 mg/dl, suggestive of acute-on-chronic renal failure for which he was managed with hemodialysis.

Discussion

Better understanding of the mechanism underlying the adverse effects, optimal dosing, and ways of monitoring drug actions is becoming increasingly important as TKIs are being prescribed more widely.

Sunitinib-associated cardiac toxicities include congestive heart failure, LVEF reduction, and hypertension [4]. However, little information is known about mechanism responsible for the cardiotoxicity. The initial publication on the pivotal phase III randomized trial of sunitinib versus interferon- α in patients with untreated mRCC reported a 10% incidence of LVEF decline to subnormal in patients treated with sunitinib. However, grade III reduction in LVEF was seen in only 2% of patients [1]. Left ventricular dysfunction is the main cardiac side effect of sunitinib and may partly be a result of the cardiomyocyte toxicity exacerbated by hypertension [5]. The first and second patients described in this report developed symptomatic cardiac complications shortly after receiving sunitinib. None of these patients had a previous history of heart failure. Therefore, the authors advocate close monitoring of patients receiving sunitinib therapy through cardiac imaging modalities such as echocardiography even in the absence of prior history of cardiac diseases [4, 6].

Renal damage is infrequently reported for sunitinib. It usually constitutes reversible mild-to-moderate proteinuria, and in some rare cases nephritic syndrome, acute renal dysfunction, proliferative or collapsing glomerulo-

nephritis, interstitial nephritis, and thrombotic microangiopathy [7]. A small number of patients being treated with TKIs develop more severe kidney dysfunction manifested by nephritic-range proteinuria and acute kidney injuries [7]. Although sunitinib therapy does not usually lead to renal dysfunction, and although many adverse renal effects of anti-VEGF therapies are manageable [7], clinicians need to be aware of the potential adverse renal effects of anti-angiogenic therapy. Close clinical and laboratory monitoring such as urine dipsticks and estimated glomerular filtration rate should be performed regularly during follow-up, especially in patients with impaired renal function.

In our recent study of 21 patients who underwent target therapy for mRCC, the objective treatment response rate for the target therapy was 43% (partial response 43%, complete response 0%), stable disease rate was 38%, and disease progression rate was 19%. On the other hand, the most frequently encountered nonhematologic toxicities in subjects who have undergone target therapy were generalized fatigue (47%), hypertension (33%), LVEF reduction (9%) and diarrhea (33%); particularly higher compared to immunochemotherapy subjects was the incidence of dermatologic adverse effects, including mucositis-stomatitis (43%) and hand-foot syndrome (38%), and high-grade occurrences severe enough to impede daily life activities were also observed in 4 of 9 (44%) and 3 of 8 (37%) cases, respectively. Hematologic toxicities associated with target therapy included anemia (38%), neutropenia (14%), and Cr elevation (19%); none of the cases involved high-grade toxicities except one high grade anemia and one Cr elevation. Among these complications, the authors report 3 severe life-threatening complications after commencing sunitinib treatment.

Sunitinib is a promising treatment option for patients with mRCC. As more becomes known regarding the benefits of anti-angiogenesis agents, greater awareness of their potential adverse events should also be exercised. Understanding the basic mechanism of action, pathophysiology and clinical implications of TKIs is crucial when providing quality care to patients receiving target therapies, especially sunitinib. Clinical judgment based on the patient's medical history and clinical status should guide appropriate monitoring and subsequent actions in response to sunitinib-induced adverse events.

References

- 1 Motzer RJ, Hutson TE, Tomczak P, et al: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; 356:115–124.
- 2 Michael F, Oliver WH, Manfred PW: Molecular therapy in urologic oncology. *Urol Int* 2007;79:1–7.
- 3 Kamba T, McDonald DM: Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer* 2007;96:1788–1795.
- 4 Khakoo AY, Kassiotis CM, Tannir N, et al: Heart failure associated with sunitinib malate: a multi-targeted receptor tyrosine kinase inhibitor. *Cancer* 2008;112:2500–2058.
- 5 Chu TF, Rupnick MA, Kerkela R, et al: Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007;370:2011–2019.
- 6 Telli ML, Witteles RM, Fisher GA, et al: Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. *Ann Oncol* 2008;19:1613–1618.
- 7 Gurevich F, Perazella MA: Renal effects of anti-angiogenesis therapy: update for the internist. *Am J Med* 2009;122:322–328.