# Management of Cardiac Adverse Events Occurring with Sunitinib Treatment

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**Abstract.** *Background: Sunitinib malate is the reference standard of care for the first-line treatment of metastatic renal cell carcinoma (mRCC). Cardiovascular adverse events (AEs) have been observed with sunitinib treatment. Here, we present the case report of a 49-year-old male patient with mRCC in whom cardiac AEs experienced during sunitinib treatment were successfully managed. The patient was at poor prognostic risk, with an Eastern Cooperative Oncology Group performance status of 3. Results: The patient was treated with sunitinib 50 mg/day (4 weeks on treatment followed by 2 weeks off treatment; Schedule 4/2) following lung and bone metastases. Cardiac AEs occurred following sunitinib initiation. These events were resolved with cardiovascular co-medication. Sunitinib improved the patient's quality of life and performance status, with a prolonged duration of treatment of 24 months. Conclusion: This case indicates that cardiac AEs should not be a barrier to the effective use of sunitinib in mRCC.*

## Case Report

Sunitinib malate is an oral, multitargeted receptor tyrosine kinase inhibitor, approved multinationally for the first-line and second-line treatment of advanced and/or metastatic renal cell carcinoma (mRCC). Sunitinib has shown substantial efficacy in the first-line treatment of mRCC (1) and is now considered the reference standard of care in this setting (2). In a randomised, phase III trial in patients with previously untreated mRCC, sunitinib was associated with median progression-free survival more than double that observed with interferon-alfa (IFN-α) (11.0 months *vs*. 5.1 months, respectively; $p<0.000001$) (3). Sunitinib was also superior to IFN-α with respect to objective response rate (47% *vs*. 12%, respectively; $p<0.000001$) (3). In addition, sunitinib was associated with median overall survival (OS) of more than 2 years in this study (26.4 months *vs*. 21.8 months for IFN-α; $p=0.051$) (3). Patients were permitted to cross over from IFN-α to sunitinib in the study. To account for this, an analysis was performed on patients who received only their on-study treatments, where median OS was found to be 28.1 months for sunitinib compared with 14.1 months for IFN-α ($p=0.0033$) (3).

Cardiovascular adverse events (AEs) have been observed with sunitinib treatment. In the phase III trial in patients with mRCC, 24% of patients treated with sunitinib reported hypertension of any grade (1). The incidence of grade 3 decline in left ventricular ejection fraction (LVEF) was similar in both the sunitinib and IFN-α groups (2% *vs*. 1%) in this trial (1). The presenting study group recently reported electrocardiogram (ECG) changes in 40.5% of patients treated with either sunitinib or the multikinase inhibitor, sorafenib (4). Here a case in which cardiac AEs experienced during sunitinib treatment were successfully managed is presented.

*Patient background.* A 49-year-old male patient underwent nephrectomy in June 2005 following diagnosis of clear-cell RCC with venous invasion but no distant metastases (pT3b, pNx, M0). In March 2006, the patient was diagnosed with mRCC with lung and bone metastases. The patient presented with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 3, increased corrected calcium (1.55 mmol/L [normal range: 1.16-1.32 mmol/L]), elevated lactate dehydrogenase (539 u/L [normal: <248 u/L]) and anaemia. He was thus considered to be at poor prognostic risk according to the Memorial Sloan-Kettering Cancer Center (MSKCC) classification (5). In addition, the patient was wheelchair-bound due to weakness and pain.

*Treatment.* Sunitinib was initiated at the end of March 2006 using the standard dose of 50 mg/day on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment)

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Table I. *Adverse events according to World Health Organization (WHO) Grades. Grades seen in this patient are shown in italics.*

| Adverse event | World Health Organization (WHO) Grades | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Cardiac troponin T | 0.03-0.05 | 0.05-<0.1 | 0.1-<0.2 | 0.2 |
| Hypotension | Changes no intervention indicated | Brief (<24h) fluid replacement or other therapy indicated | *Sustained (>24h) therapy indicated resolves without persisting physiological consequences* | Shock |
| Left ventricular systolic dysfunction | Asymptomatic EF*<60-50% | Asymptomatic EF*=50-40% | *Symptomatic heart failure, responsive to intervention EF<40-20%* | Refractory heart failure Poorly controlled EF<20% |
| Pericardial effusion | Asymptomatic | - | *Effusions with physiological consequences* | Life threatening tamponade Emergency intervention indicated |

EF, Ejection fraction.

following diagnosis of lung and bone metastases. Minor toxicities (≤ grade 2) emerging upon sunitinib treatment included slight increases in blood pressure, anaemia, neutropenia and thrombocytopenia. Following two 6-week cycles of sunitinib, the patient was admitted to hospital for severe dyspnoea. His blood pressure had reduced to 90/60 mmHg and tests revealed oedema, in addition to pleural and pericardial effusions (Table I). Reduced ejection fraction (EF) of 26%, low-voltage ECG and regional contraction disturbances were observed. Cardiac troponin was detected at a level of 0.04 ng/mL. Coronary angiography revealed no significant obstructive coronary artery disease.

The patient was prescribed an angiotensin-converting enzyme (ACE) inhibitor (lisinopril 5 mg/day initiated and increased up to 30 mg/day), diuretics (spironolactone 100 mg/day and furosemide 40 mg/day) and a β-blocker (carvedilol 6.25 mg initiated twice daily and increased up to 25 mg twice daily). Sunitinib treatment was also interrupted. After 10-days of receiving cardiovascular co-medication, complete cardiac compensation occurred, including disappearance of pericardial/pleural effusions and oedema; blood pressure was normalised. Sunitinib was resumed at a reduced dose of 25 mg/day and the patient was discharged after 3 weeks in the hospital. Sunitinib dosage was subsequently increased to 37.5 mg/day. The patient remains on ACE inhibitors and β-blockers; diuretics were stopped after 3 months of treatment.

The patient survived without mRCC disease progression for 25.0 months, ending in April 2008. The patient's OS is >31 months since the start of sunitinib treatment. These findings are significant considering the patient was initially classified at poor risk according to MSKCC criteria, with an expected PFS of only 2.5 months and OS of just 5 months according to historical data (5). Throughout sunitinib treatment, there have been continuous improvements in the patient's quality of life, determined using clinical assessments. In addition, the patient has experienced no pain and was able to walk and participate in moderate exercise programmes. As of November 2007, disappearance of lung metastases and minor remission of spinal metastases were observed and confirmed by a computed tomography scan. The patient's performance status also improved to an ECOG PS of 1.

## Discussion

In the case reported here, cardiac AEs occurred following initiation of sunitinib treatment. However, rapid improvement in cardiovascular symptoms was observed following interruption of sunitinib and initiation of cardiovascular co-medication. This enabled sunitinib treatment to be successfully resumed with the patient surviving without disease progression for 25.0 months. In addition, sunitinib treatment has resulted in an improvement in quality of life and overall performance status.

This case report illustrates that cardiac AEs observed with sunitinib were reversible after the initiation of cardiac co-medication, enabling sunitinib to be re-introduced. As a result the patient achieved prolonged survival without progression and improvements in quality of life. To enable patients with cardiac AEs to be effectively managed, and maintain oncological treatment, it is important to involve a cardiologist to provide guidance at the earliest possible opportunity. The cardiologist should be informed regarding the profile of AEs that can be expected with sunitinib, in the context of the survival benefits that this agent can provide to patients with mRCC. As well as sunitinib, cardiac AEs have been observed during treatment with several other targeted agents available for mRCC, including sorafenib and

bevacizumab (6-9). As such, addressing these AEs should be the first step to allow patients to continue oncological treatment, rather than switching to a different targeted agent that may not provide the same level of antitumour efficacy. In conclusion, this case clearly indicates that cardiac AEs should not be seen as a barrier to the effective use of sunitinib in mRCC.

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