Cardiac Magnetic Resonance Imaging in Sunitinib Malate-related Cardiomyopathy: No Late Gadolinium Enhancement

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Sunitinib malate, an oral multitargeted tyrosine kinase inhibitor (TKI), has been approved for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumors. It is supposed that this targeted approach improves antitumor activity with less toxicity than traditional chemotherapy. However, unanticipated cardiotoxicity related to TKIs has been reported. Less well described are the treatment and prognosis of patients with sunitinib-related cardiogenic shock. Here, we report a successfully treated case. In contrast to previous case reports, the shock status did not allow for standard heart failure treatment with angiotensin-converting enzyme inhibitor or beta-blocker. We used intra-aortic balloon counterpulsation, and the patient survived. Twenty-four days after onset, the patient's left ventricular ejection fraction had improved from 20% to 48%. To the best of our knowledge, this is the first case report of severe heart failure after sunitinib treatment in Taiwan. As the clinical application of TKIs expands, cardiologists and oncologists should be alert to the possible adverse cardiovascular effects and be ready to institute prompt treatment. [*J Chin Med Assoc* 2009;72(6):323–327]

Key Words: cardiac magnetic resonance imaging, heart failure, sunitinib, tyrosine kinase inhibitor

Introduction

Sunitinib malate is an oral tyrosine kinase inhibitor (TKI) that has been approved for treating renal cell carcinoma and gastrointestinal stromal tumor. Cardiotoxicity related to sunitinib, though not common, has been raising some attention. Standard treatment includes drug discontinuation, angiotensin-converting enzyme inhibitor (ACEI) and beta-blocker. In patients whose cardiac dysfunction has progressed to cardiogenic shock, treatment and prognosis are less well described in the literature. Here, we report a case of sunitinib-related cardiomyopathy and cardiogenic shock. The special features of the patient's cardiac magnetic resonance imaging (MRI) are also described.

Case Report

A 68-year-old woman with renal cell carcinoma was admitted due to progressive exertional dyspnea, general malaise and reduced appetite for 2 weeks. Four months prior to this admission, on the diagnosis of renal cell carcinoma, she underwent right radical nephroureterectomy. With inoperable residual and progressive interaortocaval lymph node disease, she was placed on sunitinib malate (37.5 mg/day for 4 weeks followed by 2 weeks off) 6 weeks prior to this admission. She had no history or clinical symptoms suggestive of coronary artery disease or other cardiovascular disease. The patient did not receive echocardiographic or other types of cardiovascular function examination before the use of sunitinib due to her good functional capacity and lack of risk factors for cardiovascular disease. Before admission, she did not have symptoms of upper airway infection and denied consumption of other drugs or alcohol.

On presentation, the patient was acutely ill-looking. She was breathing rapidly, perspiring profusely, and her extremities were cool and clammy. The jugular vein was engorged, and breath sounds revealed bilateral crackles. Her heart beat was regular and rapid. A grade II/VI apical systolic murmur was detected. Body temperature was 37.2°C, blood pressure was

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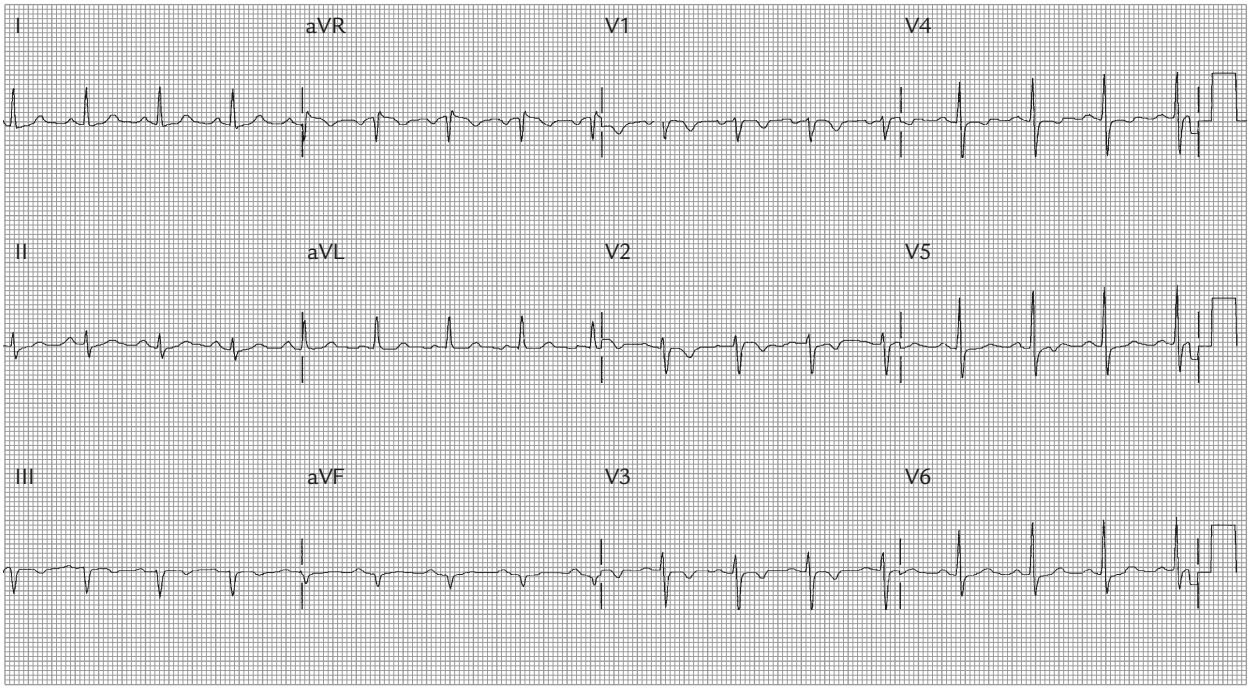

Figure 1. Twelve-lead electrocardiogram of the patient 4 months prior to the onset of heart failure, which demonstrates sinus tachycardia, left axis deviation, narrow QRS morphology with nonspecific T wave abnormalities at precordial leads V2 to V4.

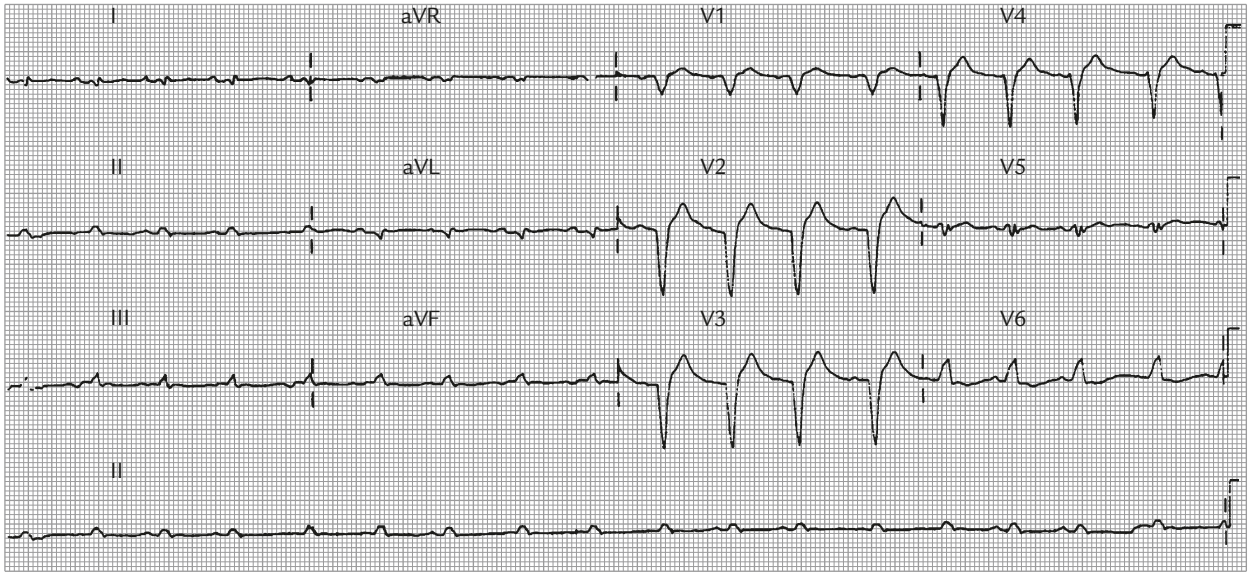

Figure 2. Twelve-lead electrocardiogram of the patient at the onset of heart failure, which demonstrates sinus rhythm and left bundle branch block. The wide QRS morphology was different from her previous electrocardiographic study.

106/68 mmHg, and pulse was 105/minute. Four months previously, electrocardiography (ECG) had shown sinus tachycardia, left axis deviation, and narrow QRS morphology with nonspecific T wave abnormalities at precordial leads V2 to V4 (Figure 1). On this admission, ECG demonstrated sinus rhythm, with wide QRS complex in the pattern of left bundle branch block (Figure 2). Chest X-ray revealed enlarged cardiac silhouette and pulmonary congestion. Echocardiography showed global hypokinesia and poor left ventricular (LV) contractility; LV ejection fraction (LVEF) was 20%. LV wall thickness was within normal limits. Cardiac biomarkers were elevated, with patterns of mainly rhabdomyolysis mixed with minor myocardial injury

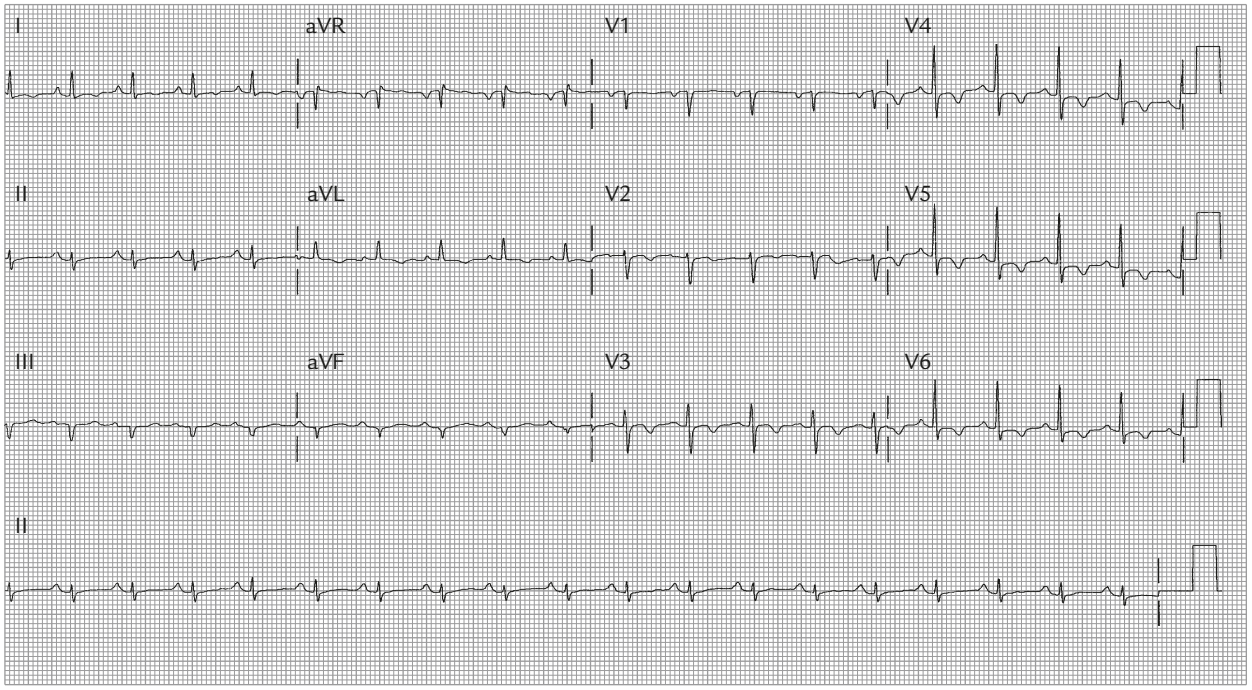

Figure 3. Twelve-lead electrocardiogram of the patient after return of cardiac contractility, which demonstrates sinus tachycardia, left axis deviation, left atrial abnormality, and narrow QRS morphology with nonspecific T wave abnormalities at leads V2 to V6 and I, aVL.

(peak enzyme levels: CPK, 10,740 IU/L; CKMB, 105 U/L; troponin-I, 2.91 ng/mL).

Despite diuretics and infusion of inotropics, digitalization and standard heart failure treatment with ACEI and aldosterone, the patient developed progressive respiratory distress and low perfusion status. Multiorgan dysfunction ensued, with acute renal failure, hepatic dysfunction, ileus and depressed consciousness. ECG revealed progressive widening QRS with no ST segment deviation. Cardiac biomarkers demonstrated no further elevation. Two days after admission, the patient was intubated and intra-aortic balloon counterpulsation (IABP) was administered, after which hemodynamic status and organ failure stabilized and gradually recovered. Ten days later, she went off IABP support and was successfully weaned off the ventilator 24 days later. LVEF improved to 48%. The subsequent ECG was similar to her baseline ECG in narrow QRS complex morphology, although more prominent left atrial abnormality was noted (Figure 3). Neither cardiac catheterization nor cardiac biopsy was performed because of the patient's family's refusal and the great improvement observed after IABP support.

For further study of her cardiac failure, cardiac MRI was performed 45 days after diagnosis. Neither resting perfusion defect nor late gadolinium enhancement (LGE) was documented (Figure 4). The patient was discharged with independent functional capacity.

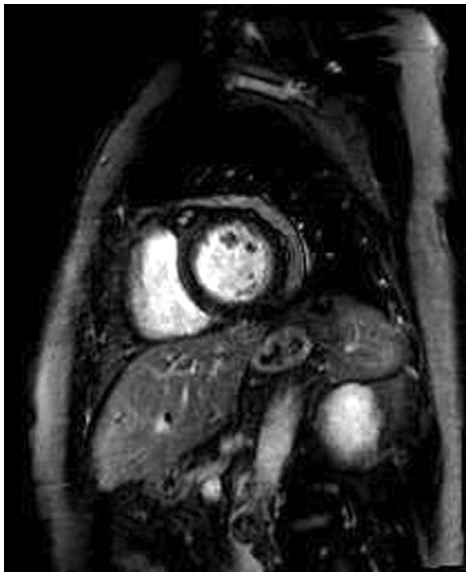

Figure 4. Cardiac magnetic resonance imaging of the patient shows no late gadolinium enhancement.

Discussion

New targeted cancer therapeutics have improved oncology practice over the last several years. Via targeted inhibition of tyrosine kinase activity, in contrast to killing all rapidly dividing cells, the new targeted drugs are expected to have more potent anticancer effects with

less toxicity compared to traditional chemotherapy. However, attention is being directed towards the development of cardiotoxicity as an "off-target" side effect. Starting from the crucial phase III trial of the anti-HER2 monoclonal antibody trastuzumab in the treatment of metastatic breast cancer,[1] to the reports of cardiotoxicity of small-molecule TKIs including lapatinib, imatinib[2] and sunitinib malate,[3] it has recently been suggested that several TKIs may be cardiotoxic and potentially lethal.

Sunitinib malate (Sutent; Pfizer, New York, NY, USA) is an oral TKI targeting vascular endothelial growth factor receptor 1–3, platelet-derived growth factor receptor α/β, FMS-like tyrosine kinase-3, colony-stimulating factor-1 receptor, and the product of the human RET oncogene. It is approved in the United States and European Union for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumors. From the phase III trial of sunitinib versus interferon-α in patients with metastatic renal cell carcinoma, sunitinib was reported to be associated with a 10% incidence of below-normal LVEF decline.[4] Most of the cardiotoxicity was reversible and not related to significant clinical sequelae. Chu et al reported that 8 of 75 patients (11%) receiving sunitinib for a median of 30.5 weeks (range, 10.7–84.9 weeks) developed adverse cardiac events,[3] including 1 patient with cardiovascular-related death, 1 patient with myocardial infarction and 6 (8%) patients with nonfatal New York Heart Association III to IV congestive heart failure. In their series, 20% developed grade 2 cardiotoxicity (any drop in LVEF < 50%) according to the definition of the National Cancer Institute's *Common Terminology Criteria for Adverse Events* (CTCAE), version 3.0.[5] From this series, it was predicted that an initial reduction of 2% LVEF from baseline would be followed by 1.5% LVEF reduction per cycle of sunitinib treatment. Telli and colleagues reported that 15% of their patients developed symptomatic LV dysfunction 22–435 days after the initiation of sunitinib.[6] Among the patients who developed sunitinib-related cardiotoxicity, 43% (3 of 7 patients) had persistent LV dysfunction after discontinuation of sunitinib and initiation of heart failure treatment. One patient (14%) died of heart failure. A history of congestive heart failure, coronary artery disease and lower body mass index were associated with increased risk of sunitinib-related cardiotoxicity.

The manifestations of sunitinib malate-related cardiac failure are not different from other causes of heart failure, and include malaise, exertional dyspnea, edema and poor appetite. However, the symptoms could wrongly be attributed to the malignancy. In our case, a vigilant oncologist led to early diagnosis. In addition to echocardiography, it is worthwhile to note that increased QRS duration and QRS morphological change on ECG with deterioration in cardiac function could be specific findings of sunitinib-related cardiomyopathy, implying conduction delay through the unhealthy myocardium. With improvement in cardiac function, the QRS duration would shorten. Thus, ECG can be incorporated into daily practice as a method of real-time cardiac follow-up in patients receiving sunitinib or other TKIs. This demands further studies focusing on this issue.

Our patient did not have a history of coronary artery disease or congestive heart failure prior to sunitinib treatment. She developed symptomatic heart failure 42 days after initiation of sunitinib, presenting with cardiogenic shock refractory to medical treatment, i.e. grade 4 cardiotoxicity according to the CTCAE, version 3.0, definition. Although most cases of sunitinib-related heart failure experience a relatively benign clinical course and will achieve a full recovery of LV function if sunitinib is discontinued and standard heart failure medications are administered, there are some case reports of severe and refractory heart failure and cardiac death.[7,8] No particular management is advised in addition to drug discontinuation and ACEI/beta-blocker. In our case, the shock status did not allow for the use of ACEI and beta-blocker. We used IABP as a mechanical support and bridge to the recovery of cardiac function over the tough conditions related to cardiogenic shock and multiorgan dysfunction. This is the first report that documents that IABP can be beneficial in severe sunitinib-related cardiotoxicity and cardiogenic shock.

The mechanisms of sunitinib-related cardiac dysfunction are not well known. Studies using mice models revealed that sunitinib had direct cardiomyocyte toxicity and induced mitochondrial damage.[3] Since the transmission electron micrographs of endomyocardial biopsy samples from patients and mice experiencing sunitinib-related cardiac dysfunction revealed mitochondrial injury (mitochondrial swelling and degenerative changes, including membrane whorls and effaced cristae) without apoptosis, it was postulated that the cardiac dysfunction is potentially fully reversible. The cardiac dysfunction is probably related to impaired ATP generation secondary to mitochondrial dysfunction instead of irreversible damage and myocyte loss. The cardiac MRI in our patient could be indirect evidence since no LGE suggestive of myocardial scarring was detected. Fallah-Rad et al reported LGE in trastuzumab-induced cardiomyopathy.[9] They demonstrated LGE of the subepicardial lateral wall as a

common finding in patients with trastuzumab-related cardiomyopathy and proposed that LGE–cardiovascular magnetic resonance could be a tool for noninvasive diagnosis and prognostic evaluation. Our report does not contradict their findings since sunitinib and trastuzumab are different types of TKI; one is a small-molecule TKI targeting both receptor and nonreceptor tyrosine kinases, the other is a monoclonal antibody targeting growth factor receptor tyrosine kinase. They are directed at different pathways in regulating cell survival and proliferation.

As the clinical application of sunitinib and other TKIs expands, cardiologists should be familiar with the potential risk of LV dysfunction related to all TKIs, especially in at-risk patients such as those with coronary artery disease or a history of heart failure.[6] As we have seen in the cases of trastuzumab in breast cancer, routine prospective cardiac monitoring with prespecified guidelines for withholding or discontinuing treatment can decrease the incidence of symptomatic heart failure.[10] It should be emphasized that thorough evaluation of patients' cardiovascular risks and cardiac performance status with ECG and echocardiography is mandatory before and during TKI administration. Whether prospective use of ACEI and/or beta-blockers can prevent TKI-related heart failure is currently under investigation.[11,12] When symptoms suggestive of potential cardiac failure occur, ECG and echocardiography are easily-available diagnostic tools. Once TKI-related cardiac failure is diagnosed, the TKI should be discontinued and medical treatment for heart failure, including ACEI and beta-blocker, promptly administered. If pumping function deteriorates, mechanical support such as IABP may be of great benefit. With prompt diagnosis and treatment, the cardiac dysfunction may be reversible and cardiac-related death avoided.

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