Acute cardiac failure after sunitinib

A 54-year-old male with cytokine-refractory metastatic renal cell carcinoma was admitted because of respiratory distress and hypotension. Five years earlier, he has been treated with alpha interferon (IFN) and interleukin-2 (two cycles of 6 weeks, s.c.) for bone, mediastinal lymph node and pulmonary metastases. Six months before admission, sunitinib (50 mg/day during 4 weeks followed by 2 weeks of rest) was initiated for disease progression and a partial response (according to Response Evaluation Criteria in Solid Tumors criteria) was obtained after 3 months. Sunitinib was well tolerated with a grade 2 fatigue (NCI—CTC version 2). As cardiovascular risks, only a well-controlled chronic hypertension (carvedilol 25 mg/day) was recorded and sunitinib did not worsen blood pressure. He did not have symptoms or past medical history of ischemic cardiomyopathy. At admission, the patient was still taking sunitinib.

The symptoms appeared 1 week before and worsened gradually. Blood pressure was 75/48 mmHg and heart rate 104 beats per minute. The patient was admitted into the intensive care unit. Chest radiograph revealed diffuse interstitial pulmonary infiltrates consistent with pulmonary edema. ECG demonstrated ST-segment elevation in D1, aVL, V5 and V6. Cardiac enzymes were abnormal: CPK, 643 IU/l (normal value <400); myocardial band, 10 mg/l (normal value <3) and Troponin-l, 2 ng/ml (normal value <0.06). Echocardiogram showed left and right ventricular dilatation. Hemodynamic data on admission showed biventricular failure (cardiac index 1.3 l/min/m², capillary wedge pressure 10 mmHg, pulmonary artery mean pressure 17 mmHg and right atrial pressure 17 mmHg) with a predominantly right ventricular dysfunction. Dobutamine infusion did not improve the hemodynamic status (after 12 h infusion at 10 g/kg/min, cardiac index remains at 1.27 l/min/m²) as well as Milrinone. This situation was thus consistent with refractory heart failure. Eight days after admission, despite optimal cardiac and respiratory supports, he died from cardiac and respiratory failure with renal and liver dysfunctions.

Post-mortem examination revealed a heart that was soft with mildly dilated atrial and ventricular chambers. The coronary arteries were normal with neither luminal narrowing nor thrombosis. No macroscopic or microscopic sign of myocardial ischemia or infarction was found. The valves were normal. The pericardium was highly fibrous and adhered to the epicardium. Three metastases were found in the lungs. The lower pole of the right kidney contained a metastatic nodule. At histology, the heart revealed a diffuse loss of cellular mass (Figure 1). The myocardial muscle bundles were fragmented and dissected by loose fibrous tissue in association with edema depleted of lymphocytic infiltration. The cytoplasm of myocardial cells was observed to be occasionally eosinophilic or vacuolized with gross anisokaryosis. These histological and cytological changes in the absence of inflammatory infiltrate were in favor of a cardiomyopathy of toxic origin.

Vascular endothelial growth factor (VEGF) has been incriminated in angiogenesis and revascularization after myocardial infarction indicating that VEGF could be an important growth factor for the cardiac tissue [1]. In addition, platelet-derived growth factor receptors (PDGFR) are also expressed on cardiomyocytes. Cardiotoxicity, however, has been rarely described with antiangiogenic therapy [2, 3].

Sunitinib is a tyrosine kinase inhibitor with a wide range of kinase inhibition, including KIT, PDGFRα/β, VEGF receptor 1–3, colony-stimulating factor 1, RET and FLT3. Sunitinib improves progression-free survival in metastatic renal cell carcinoma and imatinib-refractory gastrointestinal stroma tumors (GISTs) [2, 3].

In a large phase III trial randomizing renal cell carcinoma patients between IFN or sunitinib, decline in left ventricular ejection fraction (any grade) has been observed in 10% of sunitinib-treated patients [2]. Among them, only 2% had a grade 3 cardiotoxicity. This frequency was not statistically different than the one observed in the IFN group and all the patients recovered without sequelae. In the randomized trial comparing placebo versus sunitinib in imatinib-resistant GIST, cardiotoxicity was not found to be increased by sunitinib [3] although the prescribing information for sunitinib mentions that 11% of patients had declines in LVEF to below the lower limit of normal in this last study [4]. Two other cases of cardiac failure were identified in sunitinib dose-escalation study in acute myeloid leukemia patients [5]. One of these patients received a high daily dosage (75 mg, 4 weeks followed by 2 weeks of rest) and the other developed cardiac deficiency after myocardial infarction. Recently, Chu et al. [6] assessed the cardiovascular risk associated with sunitinib in 75 patients with GIST. Six patients (8%) had a nonfatal New York Heart Association class III–IV congestive heart failure. Left and ventricular dysfunction improved in five of these patients after sunitinib discontinuation. Mechanisms of cardiac dysfunction is incompletely understood [7] but has been recently investigated by the same group. Interestingly, they found that sunitinib had direct cardiomyocyte toxicity and induced mitochondrial injury in mice [6]. Incubation of rat
cardiomyocyte with sunitinib-induced activation of caspase-9 involved in mitochondrial apoptotic pathway [6].

In our patient, other causes of cardiac failure like ischemia, viral myocarditis or drug-induced cardiopathy were reasonably excluded since no inflammatory infiltration or vascular abnormalities were found at pathological examination. In addition, the patient did not take other drugs known to induce cardiac failure. It is still possible that the previous hypertension of our patient has favored the heart failure although blood pressure was well controlled by β blocker even after the initiation of sunitinib. In the Chu’s report, the only significant independent predictor of congestive heart failure was history of coronary disease and not hypertension [6].

Bevacizumab, a humanized mAb directed against VEGF, has not been reported to induce cardiac failure when used in monotherapy. However, when combined with anthracyclines, it seems that cardiomyopathy may be more frequent than what is expected with chemotherapy alone [8, 9]. The cardiovascular risks of the other tyrosine kinase inhibitors targeting the VEGF pathways need further investigations.

Our patient died of severe cardiac dysfunction indicating that cardiac failure induced by sunitinib can be sometimes life threatening. Oncologists should be aware of this complication and baseline and periodic evaluation of ejection fraction should be considered, especially for patients with cardiac risk factors.

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