Reversible Cardiomyopathy Associated with Sunitinib and Sorafenib

**TO THE EDITOR:** Tyrosine kinase inhibitors with potent properties against vascular endothelial growth factor (VEGF) signaling pathway (VSP inhibitors) are effective antitumor agents in metastatic renal-cell carcinoma and are now increasingly used in the treatment of other tumors. Although VSP inhibitors have been associated with cardiomyopathy, the nature of this side effect is unclear. We report two cases of severe symptomatic, yet reversible, cardiomyopathy after VSP inhibitor therapy.

A 46-year-old woman with metastatic gastrointestinal stromal tumor was started on sunitinib therapy after unsuccessful treatment with imatinib. She tolerated sunitinib well for 2 years at a dose of 25 mg once daily. The dose was increased to 37.5 mg once daily after disease progression. One month later, orthopnea and paroxysmal nocturnal dyspnea developed. An echocardiogram revealed cardiomyopathy with an ejection fraction of 25%. Sunitinib was discontinued and lisinopril was started at 5 mg once daily. Within 10 days, her symptoms had resolved, and she continued to receive lisinopril. An echocardiogram 2 months later confirmed an improved ejection fraction of 51% (Table 1).

A 71-year-old man with no previous history of cardiovascular problems was started on sorafenib at a dose of 400 mg twice daily for metastatic hepatocellular carcinoma. Four weeks later, shortness of breath and edema in the lower extremities developed. The physical examination revealed rales and an S3 gallop. An echocardiogram revealed severe hypokinesis and an ejection fraction of 26%. Sorafenib was discontinued and lisinopril was started at 2.5 mg once daily for the next 3 months. Within the first month, he was asymptomatic. An echocardiogram 3 months after the discontinuation of sorafenib showed a nearly normal ejection fraction (Table 1).

These cases highlight the reversibility of subacute cardiomyopathies induced by sunitinib and sorafenib. Both sunitinib and sorafenib (among the first of a growing number of VSP inhibitors) affect multiple receptors, including platelet-derived growth factor receptor (PDGFR) and c-kit. The mechanisms underlying cardiomyopathy associated with VSP inhibitors are probably complex and multifactorial. The inhibition of 5′ monophosphate-activated protein kinase signaling can cause reversible mitochondrial injury, and PDGFR inhibition may impair stress-induced paracrine angiogenic capacity. VEGF inhibition could lead to reduced myocardial capillary density, hypoxic signaling induction in the myocardium through the stabilization of hypoxia-inducible factor, and cardiac hibernation, as recently shown in transgenic mice. The investigation of the molecular pathogenesis associated with VSP inhibitors could assist in developing therapies that spare cardiac signaling pathways. Our cases also suggest that new methods for assessing subclinical myocardial dysfunction in patients receiving VSP inhibitors could enable earlier disease detection, facilitate prospective studies, and guide appropriate administration of both antitumor and cardioprotective medications.

### Table 1. Echocardiographic Measures during and after VSP Inhibitor Therapy.†

<table>
<thead>
<tr>
<th>Patient and Timeline</th>
<th>LVDD cm</th>
<th>LVSD cm</th>
<th>LAD cm</th>
<th>Ejection Fraction †</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During therapy with sunitinib</td>
<td>5.40</td>
<td>4.70</td>
<td>4.80</td>
<td>25</td>
</tr>
<tr>
<td>2 Months after therapy</td>
<td>4.90</td>
<td>3.50</td>
<td>3.10</td>
<td>56</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During therapy with sorafenib</td>
<td>5.60</td>
<td>4.30</td>
<td>4.30</td>
<td>26</td>
</tr>
<tr>
<td>3 Months after therapy</td>
<td>4.80</td>
<td>2.85</td>
<td>3.80</td>
<td>51</td>
</tr>
</tbody>
</table>

* LAD denotes left atrial diameter, LVDD left ventricular end-diastolic diameter, LVSD left ventricular end-systolic diameter, and VSP vascular endothelial growth factor signaling pathway.
† The ejection fraction was measured with the use of the biplane Simpson’s method.
protective therapies. This model is already being explored in patients receiving trastuzumab.5

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


CORRECTIONS

The Tumor Lysis Syndrome (August 11, 2011;365:571-4). In the first letter, from Elionoff et al. (page 571), the fourth sentence should have read, “He subsequently had acute intravascular hemolysis, with the hemoglobin level decreasing from 13.1 to 4.5 g per deciliter . . . ,” rather than “. . . from 13.1 to 4.5 mg per deciliter . . . .” The article is correct at NEJM.org.

Chronic Hypertension in Pregnancy (August 4, 2011;365:439-46). In Table 2 (page 444), some of the information listed under “Canadian (2008)” was incorrect. In the “Blood-pressure levels for treatment and goals” row, the Canadian information should have read, “Treat if blood pressure is >159 mm Hg systolic or >109 mm Hg diastolic to lower risk” and “Suggested target <156 mm Hg systolic and <106 mm Hg diastolic, but in patients with major cardiovascular risk factors, <140 mm Hg systolic and <90 mm Hg diastolic.” In the “Medications” row, the entry beginning “First-line” should have read, “Most commonly used, methyldopa and labetalol; acceptable use, other beta-blockers and calcium-channel blockers.” Also, under “Australasian (2000),” the suggested target given in the “Blood-pressure levels for treatment and goals” row should have been 120–140 mm Hg systolic, rather than 110–140 mm Hg systolic. The article is correct at NEJM.org.

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