Increased cardiotoxicity of sorafenib in sunitinib-pretreated patients with metastatic renal cell carcinoma

Sorafenib and sunitinib are the new effective drugs in the treatment of metastatic renal cell carcinoma [1]. Cardiotoxicity is relatively uncommon toxicity of these molecules. Recently, effectiveness of sequential therapy of these agents was reported in a small trial [2].

Here we report three consecutive patients with metastatic renal cell carcinoma treated with sorafenib after sunitinib failure between March and May 2007. Patients characteristics are given in Table 1. All these patients were pretreated with cytokine-based therapy and had negative history of coronary heart disease. In the beginning of sorafenib therapy, all patients had lung metastases with pleural effusion, metastases in lymph nodes and one of them had also liver and brain metastases. Patients experienced transient benefit from sunitinib, with one minor response and two disease stabilization and normalization of hypercalcemia.

All patients had normal electrocardiogram (ECG) before the administration of sorafenib. Within first 2 weeks of sorafenib therapy, two patients experienced mild chest pain and ECG revealed the signs of myocardial ischemia (coronary T in precordial leads). At this time, all patients had electrolytes within normal range. After stopping of sorafenib, these changes disappeared during the time period of 1 week. These changes were not accompanied by changes in the left ventricular ejection fraction or elevation of cardiac enzymes (CK-MB, troponin T). The third patient experienced atrial fibrillation but was successfully converted to sinus rhythm with amiodarone. However, this patient had pleural drainage due to pleural effusion as well. There was no elevation of blood pressure noted in any of these patients.

Sorafenib is known to induce acute coronary syndromes, including myocardial infarction, in 2.9% of treated patients [4]. The mechanism of cardiotoxicity of multi-kinase inhibitors is largely unknown. Very few clinical trials have examined cardiotoxicity of TKIs in a prospective fashion with predefined cardiac end points, including left ventricular function. Therefore, there is a wide gap in our knowledge regarding the types and risks of cardiotoxicity for most of these agents [5].

Because, in monotherapy, the myocardial ischemia of sorafenib and/or sunitinib is rare event, we suggest that high incidence of cardiotoxicity of sorafenib in herein reported patients is a consequence of sequential therapy. Sablin et al., in retrospective analysis, reported 68 patients treated with sorafenib after sunitinib failure, but they did not observed increased cardiotoxicity. However, they did not report the time interval between sunitinib and sorafenib administration. In our institution, totally four patients were treated with sequence of sunitinib and sorafenib till now. Signs of cardiotoxicity were not recorded in the last patient that was treated with such sequence; however, the interval between sunitinib and sorafenib administration in this patient was 7 months. We suppose that observed toxicity in our patients could, as well, be explained by short interval between administration of sunitinib and sorafenib, which lasted from 2 to 3 weeks. Sorafenib and sunitinib were tested in patient’s population pretreated with cytokine therapy, therefore we do not suppose that previous interferon therapy could participate in observed toxicity in our patients. The atrial fibrillation in our third patient could be triggered by pleural drainage, and it remains unclear what is the role of sorafenib in this setting.

Based on this experience, we suggest that observed cardiotoxicity might be the result of sorafenib given in a short time after sunitinib in sequence, as well as might represent residual sunitinib adversity. Thus, we recommend the period between administration of sunitinib and sorafenib to be of longer duration. Further research in this area is warranted.

Table 1.

<table>
<thead>
<tr>
<th>Patients no.</th>
<th>Age</th>
<th>Karnofski performance status (%)</th>
<th>Prognostic scorea</th>
<th>Previous therapy</th>
<th>Sunitinib therapy (weeks)</th>
<th>Interval between sunitinib and sorafenib (days)</th>
<th>Dose of sorafenib (mg/day)</th>
<th>Other grade 3–4 toxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>70</td>
<td>Intermediate risk</td>
<td>IFN + IL-2 + 5-FU; sunitinib</td>
<td>18</td>
<td>12</td>
<td>800</td>
<td>Mouth pain</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>60</td>
<td>Intermediate risk</td>
<td>IFN; pazopanib, sunitinib</td>
<td>16</td>
<td>17</td>
<td>800</td>
<td>Mouth pain</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>70</td>
<td>Favorable risk</td>
<td>IFN; sunitinib</td>
<td>31</td>
<td>22</td>
<td>800</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

*aAccording to Memorial Sloan-Kettering prognostic model [3]. IFN, interferon; IL-2, interleukin 2; 5-FU, 5-fluorouracil.
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references


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