The oral multitargeted kinase inhibitors (MTKI) sunitinib (SU11248, Sutent; Pfizer, New York) and sorafenib (BAY 43-9006, Nexavar; Bayer Pharmaceuticals, West Haven, CT, and Onyx Pharmaceuticals, Emeryville, CA) are increasingly used to treat malignant solid tumors. These small-molecule agents inhibit signaling through receptor tyrosine kinases such as vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor receptor, and c-KIT, among others (1). In the kidney, glomerular podocytes express VEGF and glomerular endothelial cells express VEGF receptors. Podocyte-specific deletion of a single VEGF allele causes proteinuria and capillary endotheliosis in rodents, and disrupted glomerular VEGF signaling is strongly implicated in the pathogenesis of human preeclampsia (2–4).

In the institutional review board–approved case series described here, seven patients developed a preeclampsia-like syndrome characterized by hypertension and proteinuria after starting therapy with MTKI. Patients were identified clinically after developing edema, hypertension, proteinuria, and/or hypoalbuminemia (Table 1). New or exacerbated hypertension required on average two additional antihypertensive medications and occurred on average 27 weeks after the start of therapy (range, 2–116 weeks). All seven patients developed proteinuria (average 3.8 g/g, range 1.1–10.4 g/g), with peak urine protein excretion occurring at a median of 24 weeks. There was no serologic evidence of glomerulonephritis or microangiopathic hemolytic anemia in four patients tested. In most patients, the MTKI dose was either reduced or discontinued. Subsequently, in patients with follow-up information, there was dramatic improvement (patients 1, 2, 3), with one patient whose proteinuria was not further quantified except by urinalysis (patient 7). Since 2003, at least 298 patients have been treated with sunitinib or sorafenib at our institutions; thus, the cumulative crude incidence of renal adverse events is 2.3%. However, the true prevalence of MTKI-associated renal toxicity is likely higher because patients were not routinely screened in a systematic, prospective, and long-term manner for the development of new proteinuria.

VEGF antagonism in rodents reproduces the clinical and pathologic characteristics of preeclampsia, suggesting that inhibition of glomerular VEGF receptor signaling by MTKI is a plausible mechanism to account for the renal toxic effects we observe. Additional evidence for this is that bevacizumab (Avastin; Genentech, South San Francisco, CA), a VEGF-depleting humanized monoclonal antibody, is associated with a dose-dependent risk of proteinuria and hypertension (5). The gradual rise in blood pressure observed in this series may reflect the delayed development of glomerular endotheliosis.

Hypertension and/or proteinuria are probably shared toxic effects among all antiangiogenic therapies targeting the VEGF pathway. In a phase 1 trial of the small-molecule VEGF receptor antagonist KRN951, 14 of 15 patients developed hypertension and three patients developed dose-limiting proteinuria (6). MTKI–associated renal toxic effects appear to be reversible if detected early enough. All patients starting antiangiogenic therapy should undergo a baseline urinalysis with regular surveillance throughout the course of therapy, in addition to close monitoring of blood pressure and renal function.

In patients receiving antiangiogenic therapy, the development of hypertension may be a biomarker of effective VEGF signaling inhibition and superior antitumor activity (7). Whether the development of proteinuria might also serve as a surrogate marker of antitumor efficacy is unknown. Treatment options for these life-threatening advanced cancers are limited, and optimizing safe and effective drug dosing may be critical to achieve the best therapeutic impact. Clinicians should be aware of the challenges of determining the appropriate criteria for withholding this effective anti-cancer therapy and should make use of multidisciplinary consultative input to decide how best to manage these treatment-associated toxic effects.

**References**


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**Notes**

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Table 1. Characterization of hypertension and proteinuria on sunitinib and sorafenib*

<table>
<thead>
<tr>
<th>No</th>
<th>Age/gender</th>
<th>Cancer</th>
<th>Worsening/new onset of HTN</th>
<th>MTKI</th>
<th>Cumulative dose until toxicity† (g)</th>
<th>Baseline BP‡ (mmHg)</th>
<th>Maximum BP (mmHg)</th>
<th>Peak BP§ (wk)</th>
<th>Baseline proteinuria (g/g)</th>
<th>Peak proteinuria (g/g)</th>
<th>Nadir S. albumin (g/dL)</th>
<th>Time of onset of proteinuria (wk)</th>
<th>Intervention</th>
<th>Proteinuria postintervention (g/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29/F</td>
<td>GIST</td>
<td>Yes</td>
<td>Sunitinib</td>
<td>4.2</td>
<td>118/60</td>
<td>145/60</td>
<td>16</td>
<td>Negative</td>
<td>1.9</td>
<td>2.7</td>
<td>32</td>
<td>Lowered sunitinib dose</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>79/F</td>
<td>GIST</td>
<td>Yes</td>
<td>Sunitinib</td>
<td>4.1</td>
<td>132/64</td>
<td>165/70</td>
<td>20</td>
<td>Negative</td>
<td>10.4</td>
<td>2.9</td>
<td>30</td>
<td>Stopped sunitinib</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>42/F</td>
<td>GIST</td>
<td>Yes</td>
<td>Sunitinib</td>
<td>30</td>
<td>110/70</td>
<td>154/102</td>
<td>116</td>
<td>Negative</td>
<td>1.8</td>
<td>2</td>
<td>30</td>
<td>Lowered sunitinib dose</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>42/F</td>
<td>GIST</td>
<td>Yes</td>
<td>Sunitinib</td>
<td>2.1</td>
<td>130/80</td>
<td>168/111</td>
<td>8</td>
<td>Negative</td>
<td>1.9</td>
<td>3.5</td>
<td>8</td>
<td>Continued treatment</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>42/F</td>
<td>EHE</td>
<td>Yes</td>
<td>Sorafenib f/b sunitinib</td>
<td>5.3 f/b 2.3</td>
<td>141/83</td>
<td>171/105</td>
<td>6</td>
<td>Negative</td>
<td>2.3</td>
<td>3.2</td>
<td>8</td>
<td>Stopped sunitinib</td>
<td>Not available</td>
</tr>
<tr>
<td>6</td>
<td>50/M</td>
<td>TCS</td>
<td>No</td>
<td>Sorafenib</td>
<td>68.8</td>
<td>123/81</td>
<td>120/80</td>
<td>NA</td>
<td>Negative</td>
<td>1.1</td>
<td>2.9</td>
<td>20</td>
<td>Lowered sorafenib</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>56/M</td>
<td>GIST</td>
<td>Yes</td>
<td>Sorafenib f/b sunitinib</td>
<td>11.2 f/b 3.2</td>
<td>130/82</td>
<td>152/96</td>
<td>2</td>
<td>Negative</td>
<td>7.3</td>
<td>1.8</td>
<td>24</td>
<td>Stopped sorafenib</td>
<td>3+ on UA</td>
</tr>
</tbody>
</table>

* HTN = hypertension; MTKI = multitargeted tyrosine kinase inhibitor; BP = blood pressure; g/g = gram of urine protein per gram of urine creatinine; F = female; M = male; GIST = gastrointestinal stromal tumor; EHE = epithelioid hemangio-endothelioma; f/b = followed by; NA = not applicable; TCS = teratocarcinosarcoma; UA = urinalysis.

† Toxicity defined as time of onset of proteinuria or hypertension, whichever came first.

‡ BP = average of three blood pressure readings (except patients 5, 6, and 7, who had single readings).

§ Weeks elapsed when peak blood pressure was recorded.
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