Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib

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Background: Sorafenib is an orally bioavailable vascular endothelial growth factor receptor (VEGFR) inhibitor with antitumor activity in metastatic renal cell carcinoma (RCC). Sunitinib, also a VEGFR inhibitor, induces biochemical hypothyroidism in 85% of metastatic RCC patients, the majority of whom have signs or symptoms of hypothyroidism. Hence, the incidence of thyroid function test (TFT) abnormalities in patients with metastatic RCC receiving sorafenib was investigated.

Patients and methods: Sixty-eight patients with metastatic RCC were treated with sorafenib at the Cleveland Clinic Taussig Cancer Center, and 39 patients had TFTs available.

Results: Eight patients (21%) had thyroid dysfunction possibly caused by sorafenib [seven hypothyroidism (18%) and one hyperthyroidism (3%)] and eight additional patients (21%) had findings compatible with nonthyroidal illness. Only two patients had clinical signs and symptoms secondary to thyroid dysfunction and received thyroid hormone replacement.

Conclusions: In summary, clinically significant TFT abnormalities were not common in patients treated with sorafenib, and replacement therapy was rarely indicated. TFTs should be measured before sorafenib therapy in RCC patients and subsequently only if clinically indicated.

Key words: metastatic renal cell carcinoma, sorafenib, thyroid function abnormalities

introduction

Sorafenib is an orally bioavailable multikinase inhibitor whose spectrum of inhibition includes Raf kinase; vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3; platelet-derived growth factor receptor (PDGFR) β; fms-like tyrosine kinase 3; c-Kit protein; and RET receptor tyrosine kinases [1, 2]. In a phase II randomized discontinuation study, 202 patients with advanced renal cell carcinoma (RCC) were treated with 400 mg sorafenib twice daily. The median progression-free survival (PFS) was significantly longer with sorafenib (24 weeks) than placebo (6 weeks; P = 0.0087) [3]. A phase III trial of sorafenib randomized treatment-refractory, metastatic RCC patients (n = 903) to sorafenib or placebo. The median PFS for patients receiving sorafenib was 5.5 months in sorafenib, compared with 2.8 months for the placebo group (P < 0.01) [4]. Adverse events occurring during treatment in the phase III trial were predominantly of grade 1 or 2. The most common toxic effects (all grades) were diarrhea (43%), rash (40%), fatigue (37%), hand–foot skin reactions (30%) and nausea (23%). Thyroid function abnormalities were not routinely assessed in this study. Sorafenib was approved by the Food and Drug Administration for the treatment of advanced RCC in December 2005.

Sunitinib is a small molecule tyrosine kinase inhibitor of VEGFR and PDGFRs which causes significant thyroid function test (TFT) abnormalities. In one study, 56 of 66 patients (85%) treated with sunitinib had at least one TFT abnormality consistent with hypothyroidism [5]. Seventeen of those patients developed hypothyroidism, with symptom improvement in nine patients. Sunitinib has also been reported to cause hypothyroidism in patients with gastrointestinal stromal tumors (GISTs). In a prospective observational study, 42 patients (receiving sunitinib for GIST on phase I/II trials) were studied who had normal baseline TFTs before initiation of sunitinib. After an average of 50 weeks of therapy, 15 of 42 (36%) patients developed hypothyroidism. Six of the 15 (40%) patients with hypothyroidism had one or more serum thyroid-stimulating hormone (TSH) concentration measurements <0.5 μU/ml before experiencing hypothyroidism, indicating possible thyroiditis-induced thyrotoxicosis. One overtly hypothyroid patient and one hypothyroid patient underwent sonographic evaluation of...
the thyroid. In both evaluations, thyroid tissue was not visualized, indicating atrophy. The risk for hypothyroidism was found to increase with the duration of sunitinib therapy in this study [6].

Given the mechanistic overlap between sunitinib and sorafenib, the incidence of TFT abnormality in metastatic RCC patients who received sorafenib was investigated.

**Methods**

The medical records of patients with metastatic RCC who had received sorafenib on one of five Institutional Review Board-approved clinical trials of sorafenib monotherapy at the Cleveland Clinic Taussig Cancer were reviewed. Patients who received prior sunitinib and/or had abnormal baseline TFTs upon sorafenib initiation were excluded. The TFTs carried out comprised TSH, thyroxine (T4), free thyroxine index (FTI), triiodothyronine (T3) and thyroglobulin antibodies. Symptoms and physical signs possibly associated with thyroid dysfunction were recorded. The decision to initiate thyroid replacement therapy was made by the treating physician depending upon the clinical presentation. TSH (normal: 0.400–5.500 μU/ml), T4 (normal: 5.0–11.0 μg/dl) and T3 (normal: 94–170 ng/dl) were measured with the electrochemiluminescence assay. FTI (normal: 6.0–11.0 μg/dl) was calculated based on the percentage uptake of free thyroxine (normal: 0.7–1.2%).

**Results**

From February 2004 to November 2006, 76 patients with metastatic RCC were treated with sorafenib at the Cleveland Clinic Taussig Cancer Center. All patients received sorafenib 400 mg orally twice daily continuously (one cycle comprising 4 weeks) and tumor evaluations by computed tomography (CT) scans were carried out every 8 weeks. Dose adjustment to 400 mg daily and to 400 mg every other day was undertaken dependent upon toxicity and treatment protocol requirements. Five patients had received prior sunitinib and had abnormal thyroid function abnormalities before the initiation of treatment with sorafenib and were thus excluded from further review. Three more patients were excluded from the final analysis; one patient had evidence of pituitary metastasis causing panhypopituitarism and two patients were known to be hypothyroid before initiation of therapy with sorafenib.

The demographics of the 68 patients are reported in Table 1. Most patients had received one or more prior treatments for metastatic RCC. Thirty-nine of the 68 patients had TFTs carried out while receiving sorafenib. The characteristics of patients who underwent thyroid function testing and those who did not were similar, with the exception of age; patients with abnormal TFTs tending to be older than patients who were not tested \((P = 0.006)\). In total, 16 of 39 patients (41%; 95% confidence interval: 26–58%) had one or more TFT values outside the laboratory normal reference range while receiving sorafenib. There were 10 males and six females in the group of patients with abnormal TFTs, and the median age was 68 (range 51–87). The median time to the abnormal test was 1.8 months (range 0.6–7.3). Review of medical records demonstrated, with two exceptions, that none of the patients exhibited signs and symptoms that could be solely attributed to the thyroid dysfunction.

Hypothyroidism, defined as TSH elevation above the normal range, occurred in seven of 39 patients (18%) during sorafenib therapy. Symptoms and physical signs possibly associated with thyroid dysfunction were recorded. The decision to initiate thyroid replacement therapy was made by the treating physician depending upon the clinical presentation. TSH (normal: 0.400–5.500 μU/ml), T4 (normal: 5.0–11.0 μg/dl) and T3 (normal: 94–170 ng/dl) were measured with the electrochemiluminescence assay. FTI (normal: 6.0–11.0 μg/dl) was calculated based on the percentage uptake of free thyroxine (normal: 0.7–1.2%).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Number of patients with thyroid function abnormality (n = 16)</th>
<th>Number of patients with normal thyroid function (n = 23)</th>
<th>Number of patients without thyroid function tests (n = 29)</th>
<th>(P) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Median (range)</td>
<td>68 (51–87)</td>
<td>61 (35–75)</td>
<td>59 (38–76)</td>
<td>0.03(^b)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>16</td>
<td>22</td>
<td>0.66</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td>16</td>
<td>22</td>
<td>28</td>
<td>0.57</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>15</td>
<td>19</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Chromophobe</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0.34(^c)</td>
</tr>
<tr>
<td>Clear cell + papillary</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Site of metastases(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>11</td>
<td>14</td>
<td>21</td>
<td>0.72</td>
</tr>
<tr>
<td>Lymph node</td>
<td>6</td>
<td>11</td>
<td>15</td>
<td>0.71</td>
</tr>
<tr>
<td>Bone</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>0.71</td>
</tr>
<tr>
<td>Liver</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>1.0</td>
</tr>
<tr>
<td>Brain</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.55</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>6</td>
<td>13</td>
<td>19</td>
<td>0.19</td>
</tr>
</tbody>
</table>

\(^a\)Exact chi-square test unless otherwise noted.  
\(^b\)Kruskal–Wallis test.  
\(^c\)\(P = 0.46\) for the comparison of clear cell with mixed and other histologies.  
\(^d\)Categories are not mutually exclusive.
treatment, first observed from 2 to 4 months after sorafenib initiation. The first set of TFTs for hypothyroid patients carried out after initiation of sorafenib treatment are shown in Table 2. Of these seven patients with high TSH on sorafenib treatment had TSH in the mild hypothyroid range (5.5–10.0 μU/ml). One patient exhibited a rapid course of hypothyroidism with TSH rising from 5.74 to 160.64 μU/ml, and T3 decreasing from 72 to 49 ng/dl over the course of 1.5 months. One patient had normal TSH (2.42 μU/ml) but low T3 and T4 at 4 months after starting sorafenib, and these abnormalities worsened over the next 4 months with lower T3 and T4 and abnormal TSH (9.930 μU/ml). Both these patients received levothyroxine supplementation. In these seven patients, thyroglobulin antibody was measured, which showed increased titers in two patients. Three of these patients had TFTs available after sorafenib discontinuation. Two of them had persistent TSH elevation and one patient showed normalization of TSH.

Hyperthyroidism during sorafenib treatment was identified in one of 39 patients (3%) based on low TSH and high T4/FTI and/or T3. This patient did not have baseline TFTs available, but developed symptoms compatible with hyperthyroidism—~6 weeks after initiation of sorafenib. TFTs confirmed hyperthyroidism (TSH <0.05 μU/ml, high T4/FTI and T3). At the same time the patient had significant liver test abnormalities (alanine aminotransferase >10× normal, aspartate aminotransferase >15× normal) which were attributed to sorafenib toxicity. Sorafenib was permanently discontinued and the liver abnormalities normalized in 2 months, while TSH improved but remained slightly suppressed. The patient did not receive treatment for hyperthyroidism.

Other TFT abnormalities during sorafenib treatment were identified in an additional eight patients (21%) and indicated nonthyroidal illness (sick euthyroid syndrome). Isolated low T3 was found in three cases, low T3 and slightly low TSH with normal T4 in three cases, and low T3/low T4 and low or low-normal TSH in two cases.

Table 3 demonstrates the thyroid function abnormalities of the metastatic RCC patients receiving sorafenib in comparison with those seen in those receiving sunitinib in a similar population [5].

discussion

In this retrospective cohort study of thirty-nine patients with metastatic RCC treated with sorafenib, we found that biochemical hypothyroidism occurred in 18% of the patients and hyperthyroidism in 3%. The thyroid abnormalities were usually mild and required replacement therapy in only two patients.

Normal thyroid follicular cells express VEGF and VEGFR messenger RNA (mRNA) [7–9], and VEGF is a central regulator of angiogenesis in endocrine glands [10]. In Graves’ disease, there is enhanced expression of mRNA of VEGF in addition to VEGF-1 and VEGF-2 [7]. It has been postulated that a VEGFR inhibitor could affect thyroid function by preventing binding of VEGF to normal thyroid cells and/or by impairing thyroid blood flow resulting in thyroiditis and thereby causing thyroid dysfunction. Although both sorafenib and sunitinib inhibit VEGFRs, sorafenib does not cause thyroid dysfunction as seen commonly with sunitinib. This could be related to the degree of inhibition of these receptors, although direct comparison of their receptor inhibition is imprecise [11]. Additionally, off-target effects of these promiscuous receptor inhibitors may be relevant to the differing effects seen on thyroid function. Further studies are needed to explain this observation.

The RET proto-oncogene is located on chromosome 10q11.2 and encodes a cell membrane receptor tyrosine kinase that has a crucial role in transducing growth and differentiation signals in tissues derived from the neural crest such as the adrenal medulla and thyroid C cells [12, 13]. Physiological functions of RET broadly include survival, cell growth and differentiation. As sunitinib and sorafenib both inhibit RET kinase activity, this may contribute to the hypothyroidism observed.

Among our study’s limitations are the relatively small number of patients and the lack of baseline TFTs in some patients. Also, most patients had mildly abnormal thyroid tests, which may be encountered in different stages of nonthyroidal illness and should not necessarily be attributed to sorafenib. Also, contrast given with CT scans done routinely may alter thyroid function and/or TFT.
results. Additional prospective studies are needed to define fully the incidence and clinical relevance of this thyroid toxicity in patients receiving sorafenib.

conclusion
Mild biochemical TFT abnormalities are common in patients with metastatic RCC treated with sorafenib. However, severe TFT abnormalities and/or clinical signs/symptoms of thyroid dysfunction are usually not seen, and thyroid therapy is rarely required. In contrast to sunitinib, where the high incidence and clinical relevance of thyroid dysfunction require routine monitoring, patients with metastatic RCC receiving sorafenib should have TFTs carried out before sorafenib therapy and subsequently only if clinically indicated.

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