Hypothyroidism in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib

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Sunitinib is an inhibitor of the vascular endothelial growth factor and platelet-derived growth factor receptors, and it has antitumor activity in metastatic renal cell carcinoma and gastrointestinal stromal tumors. To further investigate the fatigue associated with sunitinib therapy, thyroid function tests were performed on patients with metastatic renal cell carcinoma who were receiving sunitinib. Seventy-three patients with metastatic renal cell carcinoma were treated with sunitinib at the Cleveland Clinic Taussig Cancer Center, and 66 of them had thyroid function test results available. Fifty-six (85%) of the 66 patients had one or more abnormality in their thyroid function test results, consistent with hypothyroidism, and 47 (84%) of the 56 patients with abnormal thyroid function tests had signs and/or symptoms possibly related to hypothyroidism. Thyroid hormone replacement was undertaken in 17 patients, and symptoms improved in nine of them. Thyroid function test abnormalities appear to be common in patients with metastatic renal cell carcinoma treated with sunitinib, and routine monitoring is warranted.

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Sunitinib, an orally bioavailable oxindole, is small-molecule tyrosine kinase inhibitor for vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptors (1,2). The antitumor activity of this agent was initially established in two, sequential single-arm phase II trials in patients with cytokine-refractory metastatic renal cell carcinoma. Objective response rates to sunitinib of approximately 40% and progression-free survival of 8.2 months were observed in these trials (3,4). A subsequent, randomized phase III trial in untreated patients with metastatic renal cell carcinoma that compared sunitinib with interferon α observed a statistically significantly increased objective response rate (31% versus 6%, respectively; $P<.001$, Pearson chi-square test) and progression-free survival (11 months versus 5 months, respectively; $P<.001$, unstratified log-rank test) (5). In addition, activity of sunitinib against imatinib-resistant gastrointestinal stromal tumors led the Food and Drug Administration to approve sunitinib for treatment of imatinib-refractory gastrointestinal stromal tumor and advanced renal cell carcinoma in January 2006 (6).

Common toxic effects in the renal cell carcinoma trials of sunitinib included fatigue, diarrhea, hand/foot syndrome, stomatitis, and hypertension. Fatigue was the most common and was often the dose-limiting toxicity of sunitinib in patients with metastatic renal cell carcinoma. Fatigue in these patients prompted us to measure their thyroid function. In this report, we summarize the investigation of biochemical and clinical thyroid abnormalities in a cohort of patients with metastatic renal cell carcinoma treated with sunitinib. All patients, regardless of sex, were analyzed as a single cohort.

The medical records of patients with metastatic renal cell carcinoma enrolled in one of four institutional review board–approved clinical trials of sunitinib monotherapy were reviewed. All patients signed a written informed consent form that was approved by the institutional review board. All patients received 50 mg of sunitinib orally daily for the first 28 days of a 42-day cycle, with dose adjustment to 37.5 or 25 mg daily for toxicity, as required. Thyroid function test assessment (i.e., thyroid-stimulating hormone, T3, and T4 levels and free thyroxine index) was undertaken initially on some patients because the treating physicians suspected thyroid dysfunction and later on all patients prospectively. Thyroid hormone replacement therapy and/or more frequent thyroid function testing were undertaken at the discretion of the treating physician. The frequency and results of thyroid function tests and any signs or symptoms of thyroid dysfunction

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CONTEXT AND CAVEATS

Prior knowledge

Fatigue was the most common toxic effect in patients with metastatic renal cell carcinoma in trials of sunitinib. Thyroid dysfunction has been associated with anticancer treatment for renal cell carcinoma.

Study type

Single clinic–based case series.

Contribution

Sunitinib treatment of patients with metastatic renal cell carcinoma can cause biochemical and clinical thyroid dysfunction. Symptoms improved in some patients after thyroid hormone replacement therapy.

Implications

Thyroid function test abnormalities are common in patients with metastatic renal cell carcinoma treated with sunitinib, and routine monitoring may be of value.

Limitations

The number of patients was small and there were no control subjects, so it could not be determined whether thyroid dysfunction was associated with outcome.

were collected. An objective response, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, was recorded for all patients (7).

Between May 1, 2004, and March 31, 2006, 73 patients with metastatic renal cell carcinoma were treated with sunitinib at the Cleveland Clinic Taussig Cancer Center. The demographic characteristics of all patients treated are presented in Table 1. Sixty-six patients had thyroid function test results available, initially obtained because of the clinical suspicion of treating physicians (n = 29) and later prospectively as routine laboratory assessment performed at baseline and on day 28 of every even-numbered cycle (n = 37). All patients with thyroid function test results had metastatic renal cell carcinoma. Patients in this study were treatment naive (n = 30) or had been treated with cytokine-based therapy (n = 30) or bevacizumab (Avastin, Genentech, South San Francisco, CA)-based therapy (n = 6) and then relapsed, as required by the eligibility criteria for the clinical trials in which they participated.

Table 1. Characteristics of 73 patients with metastatic renal cell carcinoma*

Characteristics	Value
Median age, y (range)	56 (23–72)
Sex, No. (%)	
Male	55 (75)
Female	18 (25)
Eastern Cooperative Oncology Group performance status, No. (%)	
0	56 (77)
1	17 (23)
Sites of metastasis,† No. (%)	
Lung	54 (74)
Lymph node	42 (58)
Bone	32 (44)
Liver	13 (18)
Brain	4 (5)
Soft tissue	46 (63)

* All 73 patients had had a prior nephrectomy, and all tumors had clear cell histology.

† Categories are not mutually exclusive.

Table 2. Thyroid function characteristics of patients with metastatic renal cell carcinoma receiving sunitinib (n = 66)

Characteristic	Value
Median baseline TSH* (range)	2.56 mIU/L (0.8–34.8)
No. of patients with one or more TFT abnormality after treatment (%)	56 (85)
No. of patients with elevated TSH levels after treatment (%)	46 (70)
No. of patients with decreased T3 levels after treatment (%)	45 (68)
No. of patients with decreased T4 levels after treatment (%)	15 (23)
No. of patients with decreased FTI after treatment (%)	20 (30)
Median cycle of TFT abnormality development (range)	2 (1–14)

* Baseline results for TSH were available for 40 patients. TSH = thyroid-stimulating hormone; TFT = thyroid function test; FTI = free thyroxine index.

Table 2 presents the thyroid function characteristics of the patients with metastatic renal cell carcinoma who were receiving sunitinib. Median thyroid-stimulating hormone at baseline was 2.56 mIU/L (range = 0.8–34.8; a normal range is 0.40–5.50 mIU/mL). Fifty-six (85%; 95% confidence interval (CI) = 74% to 92%) of the 66 patients with test results had one or more thyroid function test abnormalities. Such abnormalities were consistent with hypothyroidism in all patients and primarily included elevation of thyroid-stimulating hormone and decreased levels of T3 and, less commonly, decreases in T4 and/or of the free thyroxine index. Thyroid function test abnormalities were detected relatively early in the treatment course (median = at cycle 2), with a broad range. There were 43 males and 13 females with abnormal thyroid function test results, with a median age of 58 years (range = 23–72 years). The demographics and disease characteristics of patients with thyroid function test abnormalities were similar to those patients without such abnormalities. Two patients had a history of well-controlled hypothyroidism before the initiation of sunitinib treatment. The thyroid function tests of these two patients were consistent with more severe hypothyroidism during therapy with sunitinib. Among patients with abnormal thyroid function tests, signs and symptoms possibly related to hypothyroidism were found in 47 patients (84%; 95% CI = 72% to 92%), including fatigue, cold intolerance, anorexia, periorbital edema, fluid retention, and changes in skin or hair. Thyroid hormone replacement was undertaken at the discretion of the treating physician (on the basis of the degree of biochemical abnormality and/or clinical symptoms) in 17 patients (30% of those with abnormal thyroid function tests, 95% CI = 19% to 44%) and resulted in resolution of biochemical abnormalities in all patients and improved symptoms in nine patients. Thyroglobulin antibodies were measured in 44 patients and were abnormal (i.e., >10.0 IU/mL) in 13 patients (30%, 95% CI = 17% to 45%; eight patients at baseline and five patients after treatment). There was no association between the presence of thyroglobulin autoantibodies and either the incidence or severity of thyroid function test abnormalities. No other thyroid autoantibodies were measured. Among the 56 patients with abnormal thyroid function test results, 55 had tumor evaluation results available. The best response as defined by RECIST criteria was partial or complete response in 26 patients (47%, 95% CI = 34% to 61%). Among the 29 patients who did not achieve an objective response, 25 (44%) had stable disease and 4 (7%) had progressive disease.

In vitro and in vivo studies (8–10) have found the expression of VEGF and VEGF receptor mRNA and protein in normal thyroid follicular cells, mediated at least in part

by thyroid-stimulating hormone. Expression of VEGF protein and its receptor has not been well characterized in human thyroid tissue, and the dependence upon VEGF for normal thyroid function is unknown. It is possible that sunitinib, a VEGF receptor inhibitor, decreases thyroid function by preventing binding of VEGF to normal thyroid cells and/or by impairing thyroid blood flow, which results in thyroiditis. This hypothesis requires prospective testing and further examination of normal thyroid tissue in a cancer population. Sunitinib-induced hypothyroidism does not appear to be specific to patients with renal cell carcinoma because prior reports (11,12) in patients with gastrointestinal stromal tumor have also noted a substantial number of patients with hypothyroidism.

Anticancer treatment in metastatic renal cell carcinoma has previously been associated with thyroid dysfunction (13–15). Development of thyroid autoantibodies has been associated with improved outcome in patients with metastatic renal cell carcinoma receiving immunotherapy, such as therapy with interleukin 2 or interferon α (13,14). Although the mechanism of this potentially enhanced response remains unclear, it may involve a treatment-induced alteration of immune responsiveness and self-tolerance. The association of hypothyroidism without autoantibodies and improved clinical outcome in patients with metastatic renal cell carcinoma receiving cytokines has been observed in some, but not all, studies (15,16). The objective response rates observed in patients with thyroid dysfunction in the present series approximate those observed in the general experience among sunitinib-treated patients with metastatic renal cell carcinoma. Thus, it cannot be determined from this small series of patients whether thyroid dysfunction is associated with clinical outcome in patients with metastatic renal cell carcinoma receiving sunitinib. This conclusion is tempered by certain study limitations, including the lack of baseline thyroid function tests in some patients, the relatively small number of total patients, and the high prevalence of biochemical hypothyroidism. Further examination of hypothyroidism, thyroid autoantibodies, and additional clinical outcome measures, such as tumor shrinkage and progression-free survival, are warranted to investigate a possible association.

In conclusion, sunitinib treatment in metastatic renal cell carcinoma patients can cause biochemical and clinical hypothyroidism. Routine monitoring of thyroid function tests is warranted, and replacement therapy should be undertaken as clinically indicated.

References

(1) Sun L, Liang C, Shirazian S, Zhou Y, Miller T, Cui J, et al. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. J Med Chem 2003;46:1116–9.

(2) Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003;9:327–37.

(3) Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:16–24.

(4) Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516–24.

(5) Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe R, et al. Phase III randomized trial of sunitinib malate (SU11248) versus interferon-alfa (IFN-α) as first-line systemic therapy for patients with metastatic renal cell carcinoma (mRCC). 2006 American Society of Clinical Oncology Annual Meeting Proceedings Pt I. Vol 24 (June 20 Suppl); 2006: LBA3.

(6) Demitri GD, van Oosterom AT, Blackstein M, Garrett C, Shah M, Heinrich M, et al. Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of SU11248 in patients (pts) following failure of imatinib for metastatic GIST. 2005 American Society of Clinical Oncology Annual Meeting Proceedings Pt I of II. Vol 23 (June 1 Suppl); 2005:4000.

(7) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.

(8) Ramsden JD. Angiogenesis in the thyroid gland. J Endocrinol 2000;166:475–80.

(9) Viglietto G, Romano A, Manzo G, Chiappetta G, Paoletti I, Califano D, et al. Upregulation of the angiogenic factors PlGF, VEGF and their receptors (Flt-1, Flk-1/KDR) by TSH in cultured thyrocytes and in the thyroid gland of thiouracil-fed rats suggest a TSH-dependent paracrine mechanism for goiter hypervascularization. Oncogene 1997;15:2687–98.

(10) Wang JF, Milosveski V, Schramek C, Fong GH, Becks GP, Hill DJ. Presence and possible role of vascular endothelial growth factor in thyroid cell growth and function. J Endocrinol 1998;157:5–12.

(11) Schoeffski P, Wolter P, Himpe U, Dychter SS, Baum CM, Prenen H, et al. Sunitinib-related thyroid dysfunction: a single-center retrospective and prospective evaluation. J Clin Oncol 2006;24:3092.

(12) Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 2006;145:660–4.

(13) Atkins MB, Mier JW, Parkinson DR, Gould JA, Berkman EM, Kaplan MM. Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. N Engl J Med 1988;318:1557–63.

(14) Franzke A, Peest D, Probst-Kepper M, Buer J, Kirchner GI, Brabant G, et al. Autoimmunity resulting from cytokine treatment predicts long-term survival in patients with metastatic renal cell cancer. J Clin Oncol 1999;17:529–33.

(15) Weijl NI, Van der Harst D, Brand A, Kooy Y, Van Luxemburg S, Schroder J, et al. Hypothyroidism during immunotherapy with interleukin-2 is associated with antithyroid antibodies and response to treatment. J Clin Oncol 1993;11:1376–83.

(16) Krouse RS, Royal RE, Heywood G, Weintraub BD, White DE, Steinberg SM, et al. Thyroid dysfunction in 281 patients with metastatic melanoma or renal carcinoma treated with interleukin-2 alone. J Immunother Emphasis Tumor Immunol 1995;18:272–8.

Notes

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