

Sunitinib-induced Thyrotoxicosis – A not so Rare Entity

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Abstract. *Background/Aim:* The tyrosine kinase inhibitor (TKI) sunitinib malate is nowadays a standard first-line treatment option for patients with metastatic clear-cell renal cell carcinoma (mRCC). The aim of this study was to evaluate the incidence and clinical course of thyrotoxicosis in our cohort of patients treated with sunitinib. *Patients and Methods:* Medical records of all patients treated with first-line sunitinib for mRCC at our Institution between November 2008 and March 2014 were retrospectively reviewed. Thyroid function was assessed after every 2 cycles of therapy, during the 2 weeks off period. *Results:* Out of the 62 included patients, hypothyroidism has developed during therapy in 12 patients (19%) and it was preceded by thyrotoxicosis in 2 (3.2%). *Conclusion:* Sunitinib-induced thyrotoxicosis (SIT), a not so rare entity, was followed by hypothyroidism. The patterns of occurrence and possible significance of SIT, as predictive marker of better treatment response to sunitinib, need to be validated in further studies.

The tyrosine kinase inhibitor (TKI) sunitinib malate is nowadays a standard first-line treatment option in patients with metastatic clear-cell renal carcinoma (mRCC) (1). Although generally well-tolerated and associated with low incidence of grade 3 and 4 toxicities, sunitinib exhibits a distinct pattern of side-effects that require monitoring and management (2). Thyroid dysfunction is frequently observed and, recently, it has been shown that not only hypothyroidism but also thyrotoxicosis may occur (3-5). Although rarely described in the literature, it seems that thyrotoxicosis is not a so rare manifestation of sunitinib therapy and its incidence might be underestimated. Data

related to the risk of sunitinib-induced thyrotoxicosis (SIT) in the literature are also limited and the mechanisms of action of the drug in these circumstances are not yet fully understood (6).

The aim of the present study is to evaluate the incidence and clinical course of thyrotoxicosis in a cohort of mRCC patients treated with sunitinib and contrast the findings with contemporary literature data.

Patients and Methods

Medical records of all patients who were treated with first-line sunitinib for mRCC at our Institution between November 2008 and March 2014 were retrospectively reviewed. Patients who received less than two cycles of therapy were excluded and 62 patients remained eligible for final analysis. To receive sunitinib, patients had to have no radiological or clinical signs of brain metastases, creatinine clearance ≥ 30 ml/min and alanine and aspartate transaminase serum levels had to be less than 5-fold increased above the upper limit of normal.

Thyroid function was assessed prior to introduction of sunitinib by evaluating the presence of thyroid-related symptoms and taking detailed medical history and, thereafter, regularly after every 2 cycles of therapy, during the 2 weeks off period (the time when patients do not take the drug, according to 4 weeks on – 2 weeks off scheme), by assessing thyroid-stimulating hormone (TSH), free triiodothyronine (FT_3) and free thyroxine (FT_4) levels. Reference ranges in our laboratory are as follows: TSH from 0.4 to 4 mIU/l, FT_3 from 2.76 to 6.45 ng/ml, FT_4 from 11.5 to 22.7 ng/ml (Siemens immulite 2000 xpi; chemiluminescence; Siemens original kits, Siemens Healthcare Diagnostics, Flanders, NJ, USA).

Results

Out of 62 included patients, hypothyroidism has developed during therapy with sunitinib in 12 (19%) and in 2 of them it was preceded by thyrotoxicosis. In both patients with thyrotoxicosis, no evidence of pre-existing thyroid disorder was found at baseline, while other diseases and medications that could cause thyroiditis were excluded. Family history was also negative for thyroid disorders and autoimmune diseases. Both patients received radiocontrast agents (which can also cause thyrotoxicosis) before CT scans at follow-up but only after thyrotoxicosis already developed.

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Patient 1. In 2003, a 42-year-old male patient underwent radical left nephrectomy due to renal adenocarcinoma. In March 2011, tumor in the upper lobe of the right kidney was registered at computerized tomography (CT scan), 38 mm in size, along with several round-shaped lesions in lungs. After resection of the right kidney and metastasectomy of 4 registered lesions in the lungs, postoperative CT scan revealed residual metastatic lung disease (lesions 6-8 mm in size scattered through both left and right lung lobes). Therapy with sunitinib was introduced, 50 mg per day (4/2 scheme). After the sixteenth cycle of therapy, the dose was reduced to 37.5 mg due to a mild episode of acute pancreatitis. Other observed side effects were arterial hypertension (grade 3), hand-foot syndrome (grade 2) and diarrhea (grade 1).

After two cycles of therapy with sunitinib SIT was registered with TSH levels of 0.077 mU/l, FT₃ 8.09 pmol/l and FT₄ 30.5 pmol/l, followed by lowered TSH and increased FT₃ and FT₄ serum levels (0.055 mU/l, 10.8 pmol/l and 34.0 pmol/l, respectively) two months later. Thyroid scintigraphy demonstrated inhomogenous, faint uptake of ^{99m}Tc pertechnetate in thyroid parenchyma. Thyroid ultrasound demonstrated mildly enlarged thyroid gland with a volume of 26 ml and mild diffuse pattern, while thyroid vascularity was not increased on color Doppler. Tiamazole anti-thyroid therapy was prescribed due to prolonged course of thyrotoxicosis (lasting up to 5 months with clinical symptoms), 10 mg daily (raised to 20 mg later on). SIT converted to hypothyroidism 6 months later with peak TSH level of 56.6 mU/l. Thiamazole was then discontinued and levothyroxine replacement therapy was introduced (the dose was gradually raised to 100 µg daily). Antibodies to thyroid peroxidase (TPO-Ab) and thyroglobulin (Tg-Ab) were negative. Patient 1 is a long-term survivor on sunitinib therapy for 33 months (22 cycles) when progression of the disease was registered at CT scan. He subsequently received second-line therapy with sorafenib, and third-line therapy with everolimus.

Patient 2. A male patient aged 55 underwent radical nephrectomy in March 2013 due to adenocarcinoma of the right kidney, 9x9 cm in size. Multiple metastatic sites were identified initially in lungs (multiple lesions), right adrenal gland and vertebrae (C2, Th3-Th6) with epidural expansion and threatening spinal cord compression. Therapy with sunitinib was initiated in April 2013 (50 mg per day, 4/2 scheme), while, during the third cycle, external palliative radiotherapy to vertebral metastases was applied (both cervical spine from C1 to C3 and thoracic spine from Th2 to Th7 received 20 Gy in 5 fractions). The third and fourth cycles were not completed entirely due to development of grade 3 side-effects (stomatitis, esophagitis and vomiting with extensive weight loss); the patient ceased taking the

drug of his own accord. The dose was, thus, reduced to 37.5 mg from the fifth cycle further on.

After four cycles of therapy, on a regular follow-up visit in the off period, SIT was detected (TSH 0.054 mU/l, FT₄ 21.1 pmol/l). Anti-TPO antibodies were negative and thyroid scintigraphy was compatible with thyroiditis. Thiamazole was not prescribed. After 3 months, thyrotoxicosis converted to hypothyroidism with peak TSH values of 89 mU/l. The patient started to take levothyroxine, initially 75 µg; later the dose was raised to 87.5 µg per day. Despite severe side-effects (arterial hypertension and hand-foot syndrome grade 2, nausea, poor appetite, weight loss, tingling all over the body, constipation and stomatitis) and non-satisfactory compliance, after every two cycles, regression of overall metastatic disease was registered. In March 2014 (after eight cycles of therapy) the patient died of pulmonary embolism as an indirect consequence of the primary disease.

Discussion

Hypothyroidism is a very common side-effect of sunitinib therapy, occurring mostly in one third up to one half of patients with incidence depending on duration of the therapy (7-11). In a previous study, we found 29.3% incidence of sunitinib-induced hypothyroidism in patients with mRCC treated with upfront sunitinib (12). Although several reports were published on this matter, the significance of hypothyroidism as a predictive marker of better treatment response to sunitinib therapy is still not clear (12-14). There are conflicting reports; those showing no prognostic significance on patient outcome and those showing significant benefit for patients who experienced sunitinib-induced hypothyroidism in terms of prolonged survival. The 19% rate of hypothyroidism of the study may seem low but is probably due to the fact that a significant proportion of patients was initiated with sunitinib and had not enough time to develop thyroid dysfunction. SIT is an additional important entity that needs to be taken into account when considering clinically-relevant TKIs' effects on the thyroid gland.

In the general population, hyperthyroidism occurs at a rate of 0.77/1,000 in women and 0.14/1,000 in men annually (15). There is no relevant data regarding the incidence of hyperthyroidism in patients taking TKIs, but in previously published studies treated with sunitinib or sorafenib suppressed TSH ranged between 3 and 24% (7-10). The comparison of the incidence of hypothyroidism and thyrotoxicosis in our and other previously published similar studies with TKIs is shown in Table I. The results of our study are comparable to the largest study published, where 3% of patients receiving sunitinib were found to have TSH suppression (10). The thyrotoxicosis/hypothyroidism ratio shows that a significant proportion of patients (6%-44%)

Table I. Comparison of incidence of thyroid dysfunction in our and similar studies.

Tumor type	TKI	Patients (N)	Thyrotoxicosis N (%)	Hypothyroidism N (%)	Thyrotoxicosis/ hypothyroidism ratio (%)	Reference
RCC	Sunitinib	17	4 (24%)	9 (53%)	44%	Shinohara et al.
RCC	Sorafenib	69	11 (16%)	46 (68%)	24%	Miyake et al.
GIST	Sunitinib	42	6 (14%)	15 (37%)	40%	Desai et al.
RCC	Sunitinib	102	3 (3%)	51 (50%)	6%	Sabatier et al.
RCC	Sunitinib	62	2 (3%)	12 (19%)	17%	Our results

RCC, Renal cell carcinoma; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor.

with hypothyroidism, as an adverse effect of sunitinib or sorafenib therapy, had thyrotoxicosis prior to development of hypothyroidism (17% in our study). Keeping this in mind, SIT should be considered as a not so rare side-effect since it is in the range of common side-effects as per definition (1–10% of patients on drug experienced SIT). There is no data regarding SIT as a predictive marker of better treatment response due to small number of reported patients (16).

We are living in the era of targeted-therapies with a large number of TKIs available in randomized clinical trials and everyday clinical practice (7, 17-18). However, in the majority of studies with TKIs, the number of patients with suppressed TSH is not reported on a regular basis and, in addition, there are different criteria defining patients on TSH suppression. The results between studies are, thus, hard to compare. This practice should be changed since SIT may be life-threatening, especially in the case of thyroid storm. It should be taken into consideration that these patients are often already weak and poly-medicated. Hence, reporting these patients on a regular basis is essential.

In 2012, approximately 337,860 patients worldwide were estimated to be diagnosed with kidney cancer (19). About 15% of them were initially presented in advanced stage with distant metastases and, on the other hand, a not negligible number of patients, almost certainly, developed distant metastases during the course of the disease (20). Some of those patients were eligible only for supportive care due to their poor performance status, while others, who live in less developed regions, did not receive proper treatment. Nevertheless, a significant proportion of patients with mRCC receive TKIs with one or more agents in sequential schedule.

Drug-induced thyrotoxicosis may be attributed to destructive thyroiditis, autoimmune events and iodine-induced thyrotoxicosis. When examining the disease's time course, it becomes obvious that symptoms can occur in weeks to months and years after the initiation of therapy (21). SIT, in our two patients, was detected after 3 and 6 months of sunitinib therapy. According to Makita and Iiri, sunitinib induces thyroid dysfunction more potently than any other TKI compound by reducing thyroid micropapillary and

vascular lumen through the inhibition of the basal activity of vascular endothelial epidermal growth factor receptor's signaling pathway in a normal thyroid (6). Due to reduced blood flow, tissue ischemia may occur leading to thyroid dysfunction. Sunitinib-induced hypothyroidism seems to be caused by destructive thyroiditis as a result of tissue ischemia and apoptosis. We speculate that the incidence of SIT is much higher than reported in the literature due to mild or subclinical thyrotoxicosis in most of the patients as most of them become hypothyroid after the thyrotoxic phase, which is a consequence of destructive thyroiditis. It is a matter of controversy why some patients develop thyrotoxicosis and others do not.

The features of SIT are similar to the ones of amiodarone-induced thyrotoxicosis type II (AIT) and, therefore, management of SIT could follow, in some instances, the guidelines for management of AIT. The characteristics of AIT are very low 24-hour radioactive iodine uptake, absence of thyroid antibodies, decreased flow on color Doppler and heterogeneous pattern on thyroid ultrasound, which all were observed in both of our patients (22-23). SIT could be distinguished from other sunitinib-induced disorders on the basis of faint uptake of ^{99m}Tc pertechnetate on thyroid scintigraphy. Treatment with sunitinib should not be interrupted in the case of thyrotoxicosis, similar as in AIT, because shorter treatment duration and lower drug dose can compromise the treatment's outcome.

The natural course of thyroiditis often resolves in hypothyroidism requiring supportive care only; however, anti-thyroid drugs can also be used, as well as corticosteroids. Sometimes, surgery may be recommended (21). Corticosteroids can be prescribed for AIT and severe side-effects of radioactive iodine treatment but can also be used in the treatment of symptomatic patients with SIT. However, their use should be limited to severe cases of thyrotoxicosis in a period before resolution of clinical and biochemical symptoms.

Our suggestion for SIT screening is measurement of TSH at baseline and after every two cycles of therapy in the off period, or even before in the case of symptomatic thyrotoxicosis. In case of suppressed TSH, FT_3 and FT_4

should be measured together with ultrasound with color Doppler and thyroid scintigraphy. After diagnosis of SIT, the use of thiamazole and corticosteroids should be discussed on individual basis and the levels of TSH, FT₃ and FT₄ should be evaluated every 4 weeks, until resolution of clinical symptoms and laboratory findings.

In conclusion, SIT, viewed on a large scale, is not a so rare entity and is usually followed by conversion to hypothyroidism. As we have just discovered the tip of the iceberg, many questions need to be answered. Are SIT, preceding hypothyroidism, and upfront hypothyroidism two different forms of the same side-effect? Do these two conditions show disparate patterns regarding management and prognosis?

It is important to assess thyroid function regularly because unrecognized SIT can significantly compromise the oncological therapy and patients' compliance. The patterns of occurrence and possible significance of SIT, as a predictive marker of better treatment efficacy, need to be validated in further studies and the management of these conditions should be implemented in prospective clinical guidelines.

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Conflicts of Interest

The Authors report no conflicts of interest.

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