Thyroid dysfunctions induced

by tyrosine kinase inhibitors.

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Abstract

Introduction: Recently, tyrosine kinase inhibitors (TKIs) have emerged as a new class of anti-cancer therapy. Although generally considered less toxic than cytotoxic chemotherapy, TKIs do have significant side effects including fatigue and hypertension. In addition, thyroid dysfunction is a well-known adverse effect of TKI.

Areas covered: This review provides a comprehensive assessment of TKI-induced thyroid dysfunctions, induced by sunitinib, sorafenib, vandetanib, motesanib, axitinib, etc. Furthermore, the potential mechanisms that result in this toxicity, the clinical meaning of thyroid dysfunction in these patients, and controversies regarding treatment with thyroid hormone therapy, will be evaluated.

Expert Opinion: Detection of TKI-induced thyroid dysfunction requires routine monitoring of thyroid function and may necessitate treatment. Potential benefits to developing thyroid dysfunction and potential harm in treating it necessitate controlled studies. Finally, if treatment is pursued, appropriate dosing and timing of thyroid hormone replacement will require prospective clinical evaluation.

Keywords: axitinib, hyperthyroidism, hypothyroidism, imatinib, sorafenib, sunitinib, thyroid cancer, thyroid dysfunctions, tyrosine kinase inhibitors, vandetanib.

1. Introduction

Recently, tyrosine kinase inhibitors (TKIs) have emerged as a new class of anti-cancer therapy. Due to increased knowledge of the molecular pathogenesis of cancer, therapeutic agents that target specific altered pathways [RET, BRAF, RAS, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) receptor (VEGFR), etc] have been developed [1]. TKIs are small compounds that affect tyrosine kinase-dependent oncogenic pathways by competing with ATP-binding sites of the tyrosine kinase (TK) catalytic domains [2]. Occupation of these sites inhibits autophosphorylation and activation of the TKs and prevents the further activation of intracellular signaling pathways. TKIs can be specific to one or several homologous TKs [3]. Several multitargeted TKIs have demonstrated significant clinical activity including sunitinib, sorafenib, etc. [4-6]. The inhibition of only one kinase receptor may induce the compensatory activation of other TKs and consequent resistance to treatment with TKIs [7]. Therefore, the simultaneous inhibition of multiple activated TKs may be the best way to approach cancer [8]. Several multitarget TKIs are now approved by the US Food and Drug Administration, EMA, etc. Sunitinib and sorafenib are approved for advanced renal cell carcinoma (RCC) [9,10]. In addition, sunitinib has also been approved for gastrointestinal stromal tumor (GIST) and pancreatic neuroendocrine tumors, whereas sorafenib is approved for hepatocellular carcinoma (HCC) [11,12]. In aggressive medullary thyroid cancer (MTC) new TKIs have been approved such as vandetanib, or cabozantinib [13], while in dedifferentiated follicular thyroid cancer sorafenib, and other new TKIs, have been evaluated [14-17]. TKIs are only one of the several drugs that interfere with thyroid homeostasis [18].

Although generally considered less toxic than cytotoxic chemotherapy, TKIs do have significant side effects including fatigue and hypertension [19,20].

In addition, thyroid dysfunction is a well-known adverse effect of TKI [21]. Detection of TKI-induced thyroid dysfunction requires routine monitoring of thyroid function and may require treatment. This review provides a comprehensive assessment of TKI-induced thyroid dysfunctions, induced by sunitinib, sorafenib, vandetanib, motesanib, axitinib, etc. Furthermore, the potential mechanisms that result in this toxicity, the clinical meaning of thyroid dysfunction in these patients, and controversies regarding treatment with thyroid hormone (TH) therapy, will be evaluated.

2. Hypothyroidism

The most frequent thyroid dysfunction induced by TKIs is hypothyroidism. A number of TKIs were reported to cause hypothyroidism (**Table 1**).

2.1 Sunitinib

Sunitinib is an oral, small-molecule, multi-targeted receptor tyrosine kinase that inihibits platelet-derived growth factor receptors (PDGFRs) and VEGFRs, and plays a role in both tumor angiogenesis and tumor cell proliferation. Sunitinib is used in the treatment of metastatic RCC (mRCC) and imatinib-resistant metastatic gastrointestinal tumors. It is administered in a four-weeks-on, two-weeks-off cycle. Hypothyroidism is frequently observed with sunitinib, with a reported incidence of 53% to 85% in retrospective studies and 36% to 46% incidence in prospective studies [22-31].

An incidence analysis was performed using 6678 sunitinib-treated patients from all 24 eligible trials. The incidence of all- and high-grade hypothyroidism was 9.8% (95% CI 7.3–12.4%) and 0.4% (95% CI 0.3–0.5%), respectively. A meta-analysis of seven randomized trials with 2787 subjects revealed a relative risk (RR) of all- and high-grade hypothyroidism of 13.95 (95% CI 6.91–28.15; p<0.00001) and 4.78 (95% CI 1.09–20.84; p=0.04), respectively. Subgroup analysis revealed a significantly higher

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incidence of all-grade hypothyroidism in patients receiving sunitinib for longer duration than in patients receiving sunitinib for shorter duration [27].

Several potential mechanisms of sunitinib induced thyroid hypothyroidism have been proposed. The high incidence of transient thyrotoxicosis prior to developing hypothyroidism suggested destructive thyroiditis [32]. However, other studies have shown recovery of thyroid stimulating hormone (TSH) values to the normal range following treatment with sunitinib [25,33]. Clinical studies of thyroid radioiodine uptake inhibition suggested an inhibition of iodide uptake [24], but *in vitro* studies showed no impairment of iodide uptake [34]. *In vitro* [23] it has been shown that sunitinib impairs peroxidase activity, but this has not yet been confirmed *in vivo*. Since sunitinib inhibits VEGFRs as a principal mechanism of its action on tumors, regression of the thyroid vascular bed induced by VEGF inhibition is the likely explanation. Mouse studies have shown glandular capillary regression with sunitinib exposure [35], suggesting that sunitinib inhibits VEGFRs inducing the regression of the thyroid vascular bed. It has been reported that thyroid volume and blood flow were both reduced on sunitinib [36]. However, another study did not detect changes in thyroid volume with ultrasonography or vascularity with echo-color Doppler between before and during sunitinib treatment [24]. It has also been shown that sunitinib inhibited TH transport mediated by the transmembrane transporter MCT8 [37]. Further studies are needed to finally elucidate the mechanism of sunitinib induced hypothyroidism.

2.2 Sorafenib

Sorafenib targets multiple kinases including BRAF, VEGFR, and RET and is approved for the treatment of advanced RCC and advanced HCC in addition to being evaluated in other tumors including lung, pancreatic, prostate, and differentiated thyroid cancer [15,38]. Incidence of thyroid dysfunction with sorafenib was much less when compared to sunitinib, ranging between 20 and 36% as evaluated in different studies [28-30]. A retrospective study of 39 patients treated with sorafenib [28] identified thyroid dysfunction attributable to the drug in 21% of patients. A prospective study in a

cohort of patients [39] suggested that hypothyroidism may occur more frequently in Japanese than in Western patients. Sorafenib-induced hypothyroidism can persist after withdrawal of treatment [40]. In a study designed to determine incidence rates of TH therapy as a surrogate for sorafenib-induced clinical hypothyroidism, 77 of 1214 sorafenib patients (6.3%) received a TH [41].

The mechanism by which sorafenib induces hypothyroidism is not yet well understood. The relationship between thyroid size (measured by computed tomography) and thyroid function in patients with RCC receiving sorafenib has been evaluated. The patients who developed "hypothyroidism", after sorafenib showed thyroid size reduction of 79 ± 13%, after 12 months [42]. In a study of 21 patients treated with sorafenib, serum free thyroxine (T4) and triiodothyronine (T3) levels, adjusted for levothyroxine (L-T4) dose per kilogram body weight, decreased by 11 and 18%, respectively, whereas TSH levels increased. The serum T3/T4 and T3/reverse T3 ratios decreased by 18 and 22%, respectively, which is compatible with increased type 3 deiodination [43].

2.3 Pazopanib

Pazopanib is a potent and selective multi-targeted receptor TKI (targeting VEGFR 1, 2, and 3, c-kit, and PDGFR) that blocks tumor growth and inhibits angiogenesis [44].

It has been approved for RCC and soft tissue sarcoma [45].

A review of the literature [46] identified thyroid dysfunction attributable to pazopanib with an incidence of 7% in patients treated for mRCC. The incidence and severity of thyroid dysfunction were explored in 578 pazopanib-treated patients participating in 3 trials, and it was found that 37 patients (6%) had elevated TSH at baseline (>5 mU/L), 167 (29%) had a TSH value of >5 mU/L during treatment. Hypothyroidism (TSH > 5– 10 mU/L, and T4 < lower normal limit) was also observed in 19 (3%) patients [47]. A randomized, double-blind, placebo-controlled Phase III study evaluated efficacy and safety of pazopanib monotherapy in treatment-naive and cytokine-pretreated patients with advanced RCC. It was found that the incidence of hypothyroidism was less than 10% [48]. A Phase III,

randomized trial compared the efficacy and safety of pazopanib vs sunitinib as first-line therapy. The prevalence of hypothyroidism in pazopanib treated patients was 12% [49]. In a retrospective study of patients with mRCC who received pazopanib hypothyroidism was observed in 18% [50].

2.4 Imatinib

Imatinib is an oral TKI with activity against RET, BCR-ABL, PDGFR, c-Fms and c-Kit. Imatinib is approved for the treatment of chronic myeloid leukemia (CML), GIST, and dermatofibrosarcoma protuberans and is being evaluated for other tumors including MTC. In a study of 11 patients (1 GIST, 10 MTC) who received imatinib, eight (who had previously undergone thyroidectomies and were on TH therapy) needed increased TH requirements while on imatinib treatment [31,51]. In another study 9 out of 15 patients with advanced MTC who received imatinib (who previously underwent total thyroidectomy) and were on TH replacement, needed increased TH requirements while on therapy. On the other hand, patients with intact thyroid glands remained euthyroid while on imatinib [52]. These studies suggest that imatinib-induced thyroid dysfunction is not due action on the thyroid gland itself. This finding was further illustrated in a study of 68 patients with CML who received imatinib [53]. All patients had intact thyroid glands; there were no observed cases of thyroid dysfunction. A case of a 59-year-old woman who was under L-T4 therapy for hypothyroidism secondary to subtotal thyroidectomy, with clinical and biochemical euthyroidism, who required an increased dose of L-T4 after starting imatinib therapy, confirmed the above mentioned concept [54].

However in another study thyroid dysfunction in Philadelphia (Ph) chromosome-positive CML patients under treatment with imatinib were detected in 25% [55].

2.5 Dasatinib

Dasatinib is a second-generation TKI with activity against BCR-ABL and sarcoma that is approved for the treatment of imatinib-resistant Ph-positive CML and Ph-positive acute lymphoblastic leukemia.

Thyroid function was retrospectively reviewed in ten patients who received dasatinib, 5 (50%) developed hypothyroidism (4 subclinical, 1 clinical), none required treatment [55].

2.6 Nilotinib

Nilotinib is a small molecule TKI approved for the treatment of imatinib-resistant Ph-positive CML. The effect of nilotinib on thyroid function tests in patients with Ph-positive CML was studied. Of 55 patients, twelve patients (22%) had thyroid function tests consistent with hypothyroidism (6 subclinical, 6 clinical) at some point during their therapy. Six (11%) patients were on thyroid medication before to starting the nilotinib therapy and did not require a change in their L-T4 dose. Eighteen (33%) patients had received interferon previously, the development of thyroid dysfunction was slightly more common in these patients although not statistically significant, suggesting that interferon is not related to the appearance of thyroid dysfunctions. Three patients treated with nilotinib had positive anti-thyroid antibodies, with an episode of hyperthyroidism preceding the development of hypothyroidism. Hypothyroidism resolved spontaneously in three of these patients [55].

More recently the case of a 76-year-old man with chronic-phase CML who suffered from severe systemic edema after introduction of nilotinib has been reported. Laboratory tests revealed hypothyroidism; the patient was euthyroid prior to introduction of nilotinib. Serum TSH was 30 μU/mL with low free T4 and free T3, confirming overt hypothyroidism; anti-thyroid antibodies were negative. Ultrasound examination showed a normal size gland, markedly decreased dyshomogeneous echotexture and slightly reduced vascularity, all compatible with thyroiditis. His edema regressed dramatically after TH replacement therapy, while continued treatment with nilotinib, and laboratory examination of thyroid function also improved markedly [56].

The mechanism by which nilotinib induces hypothyroidism remain to be investigated. In an attempt to test whether inhibition by TKIs of renal tubular MCT8 increases urinary T4 excretion, T4 in urine from

11 patients treated with imatinib, dasatinib, or nilotinib was determined. T4 excretion was not increased compared with untreated patients [37].

2.7 Vandetanib

Vandetanib is an anti-cancer drug that is approved for the treatment of MTC. It acts as a kinase inhibitor of a number of cell receptors, mainly VEGFR, EGFR, and the RET-tyrosine kinase [57-59].

Thyroid function was studied in 19 patients treated with vandetanib (100 mg) for locally advanced or metastatic hereditary MTC. All 19 patients receiving vandetanib in this study had undergone prior thyroidectomy and were receiving TH replacement before entering study. Baseline TSH data were available for 17 patients, and in these patients an increase in TSH levels was observed [5.1-fold (mean) and 7.3-fold (median) increases over baseline]. No patients were reported to have symptomatic hypothyroidism, but TH replacement therapy was increased in two patients [60].

2.8 Axitinib

Axitinib is a small molecule TKI that has been successful in clinical trials with RCC. It has received approval for use as a treatment for RCC [61]. Axitinib is investigated also in lung cancer, and other solid tumors [62].

Thyroid function was studied in 18 Japanese patients with advanced solid tumors in two Phase I trials that evaluated the safety, pharmacokinetics and antitumor activity of axitinib. Sixteen patients (89%) experienced TSH elevation. Grade 3/4 toxicities included fatigue (28%). No grade 3/4 fatigue occurred in patients who started TH replacement therapy when TSH was elevated. Thyroglobulin elevation was observed in all patients who continued treatment with axitinib for $\geq$ 3 months. Abnormal TSH correlated with exposure to axitinib [63].

In a further study, at baseline, a similar percentage of Japanese patients in the axitinib and sorafenib arms were receiving medications such as L-T4 for hypothyroidism (12 and 14%, respectively). However, during study treatment, more patients administered with axitinib were diagnosed with

hypothyroidism than those receiving sorafenib (44 and 24%, respectively). The diagnosis of hypothyroidism in either arm was more common among Japanese than in the overall population. Hypothyroidism was managed with TH replacement therapy as the protocol recommended that hypothyroidism be treated per standard medical practice to maintain euthyroid state. In the Japanese subgroup, 12% of patients received thyroid medications before starting treatment with axitinib and 48% of patients started thyroid medications or increased the dose of existing thyroid medications during treatment with axitinib. In the overall population, the corresponding values were 19 and 26%, respectively [64]. In another Phase III trial comparing axitinib with sorafenib in patients with treatment-naive mRCC, hypothyroidism was more common in axitinib treated patients (39 [21%] vs 7 [7%]) [65]. A further study reported a high prevalence of hypothyroidism in a Phase II trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell RCC [66].

2.9 Motesanib

Motesanib is an orally administered small molecule belonging to angiokinase inhibitor class which acts as an antagonist of VEGFRs, PDGFRs, and stem cell factor receptors. In 2011, it was reported that a Phase III trial did not show benefit for advanced non-squamous non-small-cell lung carcinoma [67]. The drug is separately undergoing Phase II evaluation as first-line therapy for breast cancer [68]. There have also been clinical trials for thyroid cancer [69].

In an open-label, single-group, Phase II study, 93 patients (who had progressive, locally advanced or metastatic, radioiodine-resistant differentiated thyroid cancer) were treated with 125 mg of motesanib diphosphate, administered orally once daily. All the patients had previously undergone thyroidectomies and were on TH replacement. Increased serum TSH concentrations, hypothyroidism or both were observed in 20 patients (22%). The authors suggested that alterations in the absorption or metabolism of L-T4 may explain changes in TH levels while on motesanib [70].

A Phase II study investigated the efficacy and tolerability of motesanib, in advanced MTC. Of 91 enrolled patients who received motesanib hypothyroidism was observed in 29% [71].

2.10 Tivozanib

Tivozanib blocks the activation of VEGFR 1, 2, and 3 more potently than earlier TKIs. In a Phase III study of tivozanib vs sorafenib as initial targeted therapy for patients with mRCC, incidence of hypothyroidism was higher in the tivozanib arm than in the sorafenib arm. TSH levels that were normal prior to dosing but increased to > 10 mU/L during treatment were reported for 30.1% of tivozanib subjects vs 7.0% of the patients who received sorafenib. A smaller number of tivozanib subjects had low free T3 or free T4 on or after the date that the elevations of TSH were observed (8.9% with low T3; 1.9% with low free T4), consistent with the occurrence of hypothyroidism adverse events. It is important that the incidence of hypothyroidism for sorafenib reported in this Phase III trial was lower as compared to that in earlier studies [72]. Also, in a Phase I study of tivozanib, in Japanese patients with solid tumors, among 9 patients treated, 2 reported hypothyroidism (22%) [73].

3. Hyperthyroidism

Hyperthyroidism is observed with a lower prevalence in patients treated with TKIs. A number of TKIs were reported to cause hyperthyroidism (**Table 2**).

3.1 Sunitinib

In a prospective observational cohort study that included patients with normal baseline TSH, observed while on sunitinib, for thyroid dysfunction, for a median period of 37 weeks, it was found 40% had suppressed TSH prior to the appearance of hypothyroidism, suggesting that thyroiditis could have been the possible mechanism for the subsequent development of hypothyroidism [32]. This hypothesis was confirmed by the case report of a patient with transient overt thyrotoxicosis followed by

hypothyroidism, apparently related to sunitinib therapy [74]. A series of six patients who developed thyrotoxicosis while on sunitinib for mRCC was described. Two patients developed severe thyrotoxicosis within 10 weeks after commencing sunitinib. In contrast, in the four patients who presented with later onset (16-30 weeks) thyrotoxicosis, the thyrotoxicosis was relatively mild, self-limiting and rapidly progressed to hypothyroidism. These patients experienced recurrent episodes of thyrotoxicosis in temporal relation to their cyclical sunitinib treatment. These findings reinforced the hypothesis that sunitinib-induced hypothyroidism may be a consequence of preceding thyroiditis with associated transient thyrotoxicosis [33]. A total of 24 patients treated by sunitinib for RCC were studied for thyroid function; TSH levels were below the normal range in five patients (20.8%) before or during the treatment period, suggesting the diagnosis of subclinical hyperthyroidism [75]. In seven cases, during sunitinib treatment for advanced mRCC, mild hypothyroidism developed early in the first treatment cycle, and recovered spontaneously. Transient hyperthyroidism was observed during the second or third treatment cycles and was preceded by a rapid increase in thyroglobulin levels. (99m)Tc scintigraphy in the hyperthyroid state showed decreased thyroidal uptake of (99m)TcO(4)(-), suggesting destructive thyroiditis. Hypothyroidism subsequently developed, requiring L-T4 replacement therapy. Ultrasonography showed a hypoechogenic pattern of the parenchyma and decreased intrathyroidal blood flow. The thyroid glands ultimately became atrophic, which may progress to permanent hypothyroidism. These findings suggest that sunitinib-induced hypothyroidism may occur frequently and may be a consequence of thyroiditis with transient thyrotoxicosis [76]. Another case report showed a patient with RCC who developed transient overt thyrotoxicosis followed by hypothyroidism due to sunitinib treatment [77]. Four patients developed hyperthyroidism after the treatments with sunitinib. Their hyperthyroidism was diagnosed as destructive thyroiditis-induced thyrotoxicosis based on the clinical course (thyroid functions subsequently became normal without any treatment in all patients) and/or negative thyroid receptor antibodies measured in a patient. Of the four

patients who developed hyperthyroidism after treatment with sunitinib, three had hypothyroidism before the treatment [78]. The above mentioned studies suggest that hyperthyroidism may be related to destructive thyroiditis in the course of sunitinib treatment, and it is frequently followed by hypothyroidism.

3.2 Sorafenib

Among sixty-eight patients with mRCC treated with sorafenib, 39 patients had thyroid function tests available, eight patients (21%) had thyroid dysfunction possibly caused by sorafenib [seven hypothyroidism (18%) and one hyperthyroidism (3%)] [28].

Another study reported two patients who developed temporary hyperthyroidism during the course of sorafenib treatment for HCC, which was followed by overt and subclinical hypothyroidism, respectively. Thyroid ultrasonography showed an atrophic thyroid gland in patient 1, and signs of thyroiditis in patient 2. Detailed reassessment of thyroid volumes on routinely performed CT scans showed a gradual decrease in thyroid volume during sorafenib treatment in one patient, suggesting progressive thyroid destruction [79]. Another case report describes hyperthyroidism and thyroid autoimmunity induced by sorafenib in mRCC [80]. A case of sorafenib induced thyroid storm has been also reported [81].

The above mentioned studies suggest that hyperthyroidism may be related to destructive thyroiditis in the course of sorafenib treatment, and it is frequently followed by hypothyroidism. Only rarely hyperthyroidism induced by sorafenib needs to be treated.

3.3 Axitinib

Among six patients treated with axitinib for mRCC transient thyrotoxicosis due to destructive thyroiditis occurred in five patients within 7 months of treatment. Four patients exhibited both hyper- and hypothyroidism [82].

4. Clinical impact of TKI induced thyroid dysfunction

Many data suggest TKI induced thyroid dysfunction may have a prognostic value. Wolter et al. prospectively evaluated thyroid function in patients receiving sunitinib for advanced RCC [83]. The median progression-free survival (PFS) was 3.6 months when thyroid function tests remained within normal limits and 10.3 months when abnormal thyroid function tests were noted. The median overall survival was 6.6 months in patients with normal thyroid function tests and 18.2 months in patients with abnormal thyroid function tests [83]. In a Japanese study of 14 patients with mRCC who were treated with sunitinib, the tumor response rate was 73% (8/11) in patients with hypothyroidism and 33% (1/3) in patients who remained euthyroid [84]. A prospective analysis of 87 patients with mRCC who received treatment with sunitinib or sorafenib [30] confirmed the above mentioned data. Subclinical hypothyroidism was present in five patients at baseline and was diagnosed in 30 patients (36.1%) within the first 2 months of therapy. Patients with subclinical hypothyroidism had a statistically significant objective remission rate of 28.3% vs 3.3% in euthyroid patients and increase of median duration of survival [30]. Another study evaluated patients with mRCC who received sunitinib or sorafenib [31]. Twenty-one of 66 evaluable patients (31.8%) developed hypothyroidism. Hypothyroidism was associated with a longer PFS (16.0 +/− 0.8 months vs 6.0 +/− 0.8 months, p = 0.032). Hypothyroidism was found to be an independent prognostic predictor of survival in multivariate analysis [31]. Among thirty-one consecutive patients with clear cell mRCC treated with sunitinib, hypothyroidism occurred in 16 patients (52%) within 3 months (range 0.7-22.9) of treatment initiation. Thyroid replacement corrected TSH below the upper normal limit in 10 patients (63%). The hypothyroid patients tended to have longer PFS (median 12.2 vs 9.4 months; p = 0.234) and longer survival (median 22.4 vs 13.9 months; p = 0.234) than the euthyroid patients [85].

The observed correlation between the development of hypothyroidism and improved survival with TKI therapy may suggest a potential relationship between hypothyroidism and decreased cancer growth.

It might be speculated that cancer growth decreases because of reduced TKI metabolism and subsequent drug accumulation in patients with hypothyroidism.

It has been also suggested that patients developing thyroid dysfunction might tend to have their cancer better controlled through the common antiangiogenic effects affecting both the tumor and the thyroid [21]. The above mentioned studies suggest a correlation between the development of hypothyroidism and a better prognosis, but several questions are still unanswered, such as whether the time course to hypothyroidism would predict response to cancer therapy, and whether developing hypothyroidism soon after therapy or later on would affect clinical response.

5. Treatment of tyrosine kinase inhibitors associated thyroid dysfunction

There are still no guidelines regarding the frequency of thyroid function tests monitoring and treatment of thyroid dysfunctions induced by TKIs. As a reasonable guideline, the determination of serum TSH concentration on day 1 of each cycle has been suggested, but this has not been proven [84]. Wolter et al. proposed measuring TSH on days 1 and 28 of the first 4 cycles of sunitinib because most thyroid function tests abnormalities were noted to occur in the first cycles. Moreover, he suggested that patients with normal TSH values after the first 4 cycles can have their TSH measured on day 28 of every 3rd cycle [25]. Patients with preexisting thyroid abnormalities, on TH replacement, may need increased requirements [40,86]. About the level of TSH elevation that warrants treatment, the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society recommend TH to be initiated when TSH rises to a level above 10 μU/mL, but data is lacking with regard to treatment of TSH between 4.0 and 10. Wolter et al. recommended TH replacement if

circulating TSH exceeded 10 μU/mL on day 1 of a cycle of sunitinib therapy, and he warned against TH replacement based on results of thyroid function tests on day 28, since this may lead to overtreatment at the end of treatment [25]. In addition, Garfield et al. cautioned against the routine use of TH replacement, as it could induce tumor growth in patients with active cancers, in fact, it has been suggested that hypothyroidism in these patients was protective [87].

However, a study by Bladou et al. compared PFS in patients treated for thyroid dysfunction developing with sunitinib therapy with respect to those not treated. The authors noted that PFS was not different between the two groups (p = 0.94). Therefore, the relationship between exogenous TH and cancer growth is still not yet established. Other trials are needed to further investigate whether TH replacement would affect cancer outcomes [88].

6. Conclusion

TKIs belong to a new class of molecular multitargeted anticancer therapy which targets different growth factor receptors (RET, BRAF, RAS, EGFR, VEGFR, etc). They are currently used for treatment of aggressive RCC, HCC and GIST tumors, thyroid cancer, etc. A number of reports have demonstrated that TKIs can induce hypothyroidism, which was especially more common with sunitinib, sorafenib, axitinib, and vandetanib (**Table 3**). Hyperthyroidism, mainly subclinical and transitory, has been reported also with sunitinib, sorafenib and axitinib. Many mechanisms have been proposed to explain the induction of thyroid dysfunction, including the induction of thyroiditis, capillary regression in the thyroid gland, antithyroid peroxidase antibody production, and their ability to decrease iodine uptake by the thyroid gland. Clinical studies suggest that TKI-induced thyroid dysfunction may be protective as it was shown to improve overall survival. Follow-up on thyroid function tests in patients

treated with TKIs is recommended. When thyroid dysfunction occurs, appropriate treatment depends on patients symptoms and hormonal evaluation.

7. Expert Opinion

TKIs belong to a new class of molecular multitargeted anticancer therapy which targets different growth factor receptors (RET, BRAF, RAS, EGFR, VEGFR, etc). They are currently used for treatment of aggressive RCC, HCC and GIST tumors, thyroid cancer, etc. A number of reports have demonstrated that TKIs can induce thyroid dysfunctions. A number of reports have demonstrated that TKIs can induce hypothyroidism. Hypothyroidism is frequently observed with sunitinib, with a reported incidence of 53% to 85% in retrospective studies and 36% to 46% incidence in prospective studies. Incidence of thyroid dysfunction with sorafenib was much less when compared to sunitinib, ranging between 20 and 36% as evaluated in different studies; also for sorafenib the most frequently reported thyroid dysfunction was hypothyroidism. Imatinib has been shown to cause increased TH requirements in patients after thyroidectomy; while patients with intact thyroid glands remained euthyroid while on imatinib. Also for vandetanib an increase in TSH levels was observed in patients after thyroidectomy receiving TH replacement. Hypothyroidism in axitinib treated patients is about 20%. Hypothyroidism has been also reported in association with the treatments with pazopanib, motesanib, nilotinib or tivozanib. Detection of TKI-induced thyroid dysfunctions requires routine monitoring of thyroid function and may necessitate treatment. Serum TSH concentration on day 1 of each cycle has been suggested as a reasonable guideline to detect thyroid dysfunctions. Patients with preexisting thyroid abnormalities, on TH replacement, may need increased TH requirements. About the level of TSH elevation that warrants treatment, the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society recommend TH to be initiated

when TSH rises to a level above 10 μU/mL, but data is lacking with regard to treatment of TSH between 4.0 and 10 μU/mL. Some studies cautioned against the routine use of TH replacement, as it could induce tumor growth in patients with active cancers other than thyroid cancer, in fact, it has been suggested that hypothyroidism in these patients was protective. Hyperthyroidism has been reported also with sunitinib, sorafenib and axitinib, but it is mainly subclinical and transitory. In prospective observational cohort studies that included patients with normal baseline TSH, observed while on sunitinib, for thyroid dysfunction, it was found 40% had suppressed TSH prior to the appearance of hypothyroidism, suggesting that thyroiditis could have been the possible mechanism for the subsequent development of hypothyroidism. It has been also shown that during sorafenib treatment hyperthyroidism may be related to destructive thyroiditis, and it is frequently followed by hypothyroidism. Only rarely hyperthyroidism induced by sorafenib needs to be treated. Several potential mechanisms of TKIs induced thyroid dysfunctions have been proposed. The high incidence of transient thyrotoxicosis prior to developing hypothyroidism suggested destructive thyroiditis. However, other studies have shown thyroid radioiodine uptake inhibition, impairment of peroxidase activity, regression of the thyroid vascular, or inhibition of thyroid hormone transport mediated by the transmembrane transporter MCT8, by TKIs. Further studies are needed to finally elucidate the mechanism of TKIs induced dysfunctions.

Potential benefits to developing thyroid dysfunctions and potential harm in treating it necessitate controlled studies. Finally, if treatment is pursued, appropriate dosing and timing of thyroid hormone replacement would require prospective clinical evaluation.

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Article Highlights Box

1. TKIs do have significant side effects including fatigue and hypertension; in particular thyroid dysfunction is a well-known adverse effect of TKIs.

2. The most frequent thyroid dysfunction induced by TKIs is hypothyroidism.

3. It is recommended TH to be initiated when TSH rises above 10 µU/mL, but data is lacking with regard to treatment of TSH **levels** between 4.0 and 10.

4. Hyperthyroidism is frequently related to destructive thyroiditis, and followed by hypothyroidism.

5. Follow-up on thyroid function tests in patients treated with TKIs is recommended. **TSH concentrations on day** 1 of each cycle has been suggested.

6. When thyroid dysfunction occurs, appropriate treatment depends on **the patient's individual** symptoms and hormonal evaluation.

Table 1. Prevalence of hypothyroidism in patients treated with different tyrosine kinase inhibitors.

Drug	*Prevalence Range*
Sunitinib	36-85%
Sorafenib	18-36.1%
Pazopanib	3-18%
Imatinib	25%
Dasatinib	50%
Nilotinib	22%
Vandetanib	89.47%
Axitinib	12-89%
Motesanib	22-29%
Tivozanib	22-30.1%

Table 2. Prevalence of hyperthyroidism for different tyrosine kinase inhibitors used.

Drug	Prevalence Range
Sunitinib	19-40%
Sorafenib	3%
Axitinib	67%

Table 3. Drugs, relative molecular targets, and thyroid disorders related to each one.

Agent	Molecular targets	Reported thyroid disorders
Sunitinib	VEGFR-2, PDGFR, c-KIT, RET, CSF-1R, FLT3	Hypothyroidism Transient thyrotoxicosis prior to developing hypothyroidism Subclinical hyperthyroidism Transient hyperthyroidism
Sorafenib	RAF, VEGFR-1 and -2, RET, PDGFR, c-KIT	Hypothyroidism Temporary hyperthyroidism Hyperthyroidism
Pazopanib	VEGFR-1, -2, -3, PDGFR, c-KIT	Hypothyroidism
Imatinib	Bcr-abl, RET, PDGFR, c-KIT	Hypothyroidism
Dasatinib	BCR/Abl, Src, c-Kit, ephrin receptors,	Hypothyroidism
Nilotinib	BCR/Abl, KIT, LCK, EPHA3, EPHA8, DDR1, DDR2, PDGFRB, MAPK11, ZAK	Hypothyroidism Thyroiditis
Vandetanib	VEGFR-2, VEGFR-3, RET, EGFR	Hypothyroidism
Axitinib	VEGFR-1,	Hypothyroidism

	-2, and -3, PDGFR, c-KIT	Transient thyrotoxicosis Hyperthyroidism
Motesanib	VEGFR-1, -2, -3, PDGFR, c-KIT	Hypothyroidism
Tivozanib	VEGFR-1, -2, -3	Hypothyroidism