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Tyrosine Kinase Inhibitors and Thyroid Toxicity

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Some multithyrosine kinase inhibitors have been reported to cause changes in thyroid function. For the management of sunitinib-induced hypothyroidism, an evaluation of thyroid hormone and antibody profile is recommended before starting treatment with tyrosine kinase inhibitors. Patients with pre-existing thyroid dysfunction should undergo dose adjustment of L-thyroxine during treatment with tyrosine kinase inhibitors. Thyroid dysfunction is not a reason to discontinue or reduce the dosage of sunitinib. Their occurrence appears to correlate with increased antitumour efficacy of the inhibitor. There are currently no guidelines for monitoring thyroid activity during treatment with TKIs, and the time interval at which TSH should be periodically measured has not yet been determined. A reasonable approach is to monitor thyroid function, both before and during 2-4 weeks after the end of therapy. A comprehensive analysis of adverse events associated with the use of these inhibitors could help clinical monitoring of patients along with the adoption of appropriate management approaches.

Keywords: Thyroid dysfunction; tyrosine kinase inhibitors; sunitinib.

In recent years, the widespread use of tyrosine kinase inhibitors (TKIs) in oncology, either in combination with chemotherapy or radiotherapy or as a single agent, has led to a growing interest in the effects determined by these drugs on the endocrine system, on thyroid function. Dysregulation of tyrosine kinase receptor activity is a crucial event that determines the 'escape' of the tumour cell from the regulation of physiological growth mechanisms, leading to tumor genesis. The receptors 'targeted' by TKIs are implicated in cell survival, proliferation, invasiveness, and tumour angiogenesis. The tolerability profile of each molecule is variable and in comparison, to conventional cytotoxic agents, TKIs are associated with a lower degree of toxicity. Several tyrosine kinase inhibitor drugs have been approved and are used in therapy [1,2]. As a result, the use of these drugs has increased and new side effects associated with them have been highlighted. TKIs induce thyroid dysfunction and manifest in various forms such as hypothyroidism, thyroiditis, and hyperthyroidism. The most common is hypothyroidism, which can be diagnosed or remains at subclinical levels [3-5]. Sunitinib is particularly associated with these side effects that are related to thyroid function. Retrospective studies indicate that with sunitinib use there is a 53-85% risk of hypothyroidism while prospective data report an incidence of hypothyroidism of 36-71%. Other TKIs such as sorafenib, imatinib, and vandetanib induce thyroid dysfunction, though to a lesser extent than sunitinib [6-8].

TKIs and thyroid dysfunction

The main drugs believed to cause thyroid dysfunction are described and their incidences are analysed.

Sunitinib

The use of sunitinib has been associated with the highest risk of developing hypothyroidism [9]. This drug is an orally administered TKI and has multitarget activity involving the platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), kit, and RET (Table 1)[10,11].

Sunitinib treatment resulted in thyroid dysfunction after two cases experienced symptoms such as marked asthenia, confusion, decreased cold/heat tolerance, palpitations, decreased heat tolerance, and neck pain after sunitinib treatment. Both patients had subnormal serum thyroid-stimulating hormone (TSH) levels and received thyroid hormone replacement therapy, which resulted in resolution of symptoms and physiologic levels of TSH [12,13].

These clinical observations prompted prospective studies to identify possible associations between sunitinib and the development of thyroid dysfunction. Thus, data from 42 imatinib-resistant GIST gastrointestinal stromal tumour patients who had been treated with for at least three cycles of sunitinib were analysed. These patients had normal serum TSH levels and were not taking thyroid medications or drugs that may cause thyroid dysfunction. The data collected showed abnormal serum TSH concentrations in 26 patients (62%); persistent primary hypothyroidism was registered in 15 patients (36%); 4 patients (10%) developed isolated TSH suppression; in 7 patients (17%) a transient TSH increase was observed; biochemical data showed no signs of autoimmune thyroid disease in any patient [12].

There are many other studies showing a close association between sunitinib treatment and thyroid dysfunction. The conclusions to be drawn from these are: a) The longer the sunitinib treatment, the higher the risk of hypothyroidism. b) After discontinuing sunitinib, serum TSH levels return to normal over approximately 60 days [6]. The average time to develop thyroid dysfunction is about 4 weeks. Patients who did not develop hypothyroidism in the first cycle did not develop hypothyroidism in the more advanced stages of treatment. [14,15].

Sorafenib

Sorafenib is an orally administered TKI with inhibitory activity on several kinases such as BRAF, VEGFR, RET [16,17]. Because of the increased risk of thyroid dysfunction in patients receiving sunitinib, several studies have been conducted to investigate the association of other TKIs with this type of dysfunction [18,19].

These include a retrospective study evaluating thyroid function testing in patients receiving sorafenib for metastatic renal cell carcinoma (RCC). Results showed that of the 39 patients, 8 (21%) developed hypothyroidism and 7 hypothyroidism and hyperthyroidism. Clinical events due to thyroid dysfunction requiring thyroid hormone replacement therapy occurred in only 2 subjects [20]. Another study involved 38 patients, with metastatic RCC treated with sorafenib 400 mg administered twice daily, in whom thyroid function was monitored over time. Thyroid hormones were assessed before starting treatment and on the first day of each treatment cycle. Of the 38 patients, 23 had normal baseline thyroid function and 15 had thyroid dysfunction. The results showed that among the 23 patients with normal basal thyroid hormones, high serum TSH was present in 7 patients (30%), and low serum TSH in 1 patient (5%). No additional treatment had to be initiated. Of the 15 patients with basal thyroid insufficiency, two patients, whose initial condition was subclinical hypothyroidism (elevated serum TSH but normal T3 and T4), subsequently showed clinical signs of hypothiroidism. Thyroid hormone therapy had to be initiated in these patients [6, 21-23].

Imatinib

Imatinib is an oral TKI that activates with RET, BCR-ABL, PDGFR, c-Fms, and c-Kit. In a study of imatinib treatment for advanced medullary thyroid cancer (MTC) in 15 patients, 10 of whom had undergone total thyroidectomy and were receiving hormone replacement therapy, 9 patients developed hypothyroidism (the 10th patient had unmonitored thyroid function). Studies have shown that a mean 210% (range 150-350%) increase in hormone replacement therapy is required to normalize TSH levels immediately after starting treatment. Normal function was maintained in patients with intact thyroid [24, 25].

Other studies have reported similar results, suggesting that the effect of imatinib on thyroid function is relevant only to patients who have undergone total thyroidectomy, as it appears that the action of imatinib does not occur in the

thyroid itself [6,26]. For further confirmation, a study with imatinib in patients with chronic myeloid leukemia and normal thyroid function reported no cases of thyroid changes [27].

Nilotinib

Nilotinib has received clinical approval for the treatment of Philadelphia-positive chronic myeloid leukemia form (Ph-positive CML). It belongs to the second generation of TKIs, designed on the structural analogy with imatinib but provided with enhanced efficacy on BCR-ABL inhibitory power [6,28-30].

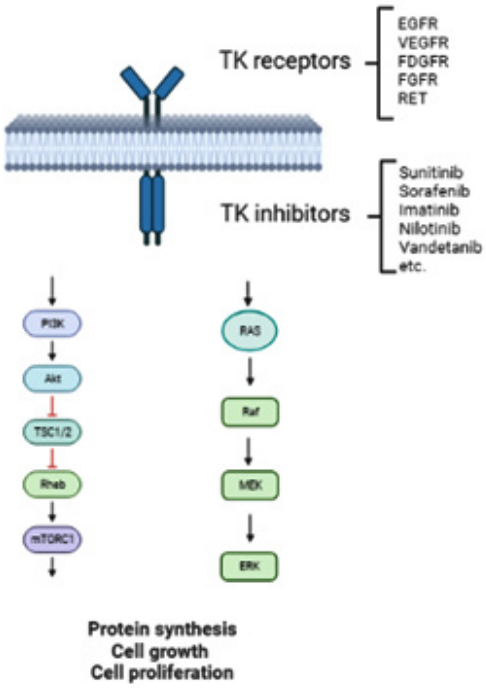

Fig. 1. Summary of the TKI effects

A retrospective study evaluated the effect of nilotinib on thyroid function in Ph-positive CML patients. Of the 55 patients, 6 (11%) were taking thyroid medication prior to initiating nilotinib therapy, and 18 (33%) had previously been treated with interferon. The results showed that: 12 patients (22%) developed hypothyroidism (6 subclinical, 6 clinical); 18 subjects (33%) developed hyperthyroidism (10 subclinical, 8 clinical). In most patients treated with thyroid hormone replacement therapy prior to initiating nilotinib, it is not necessary to change the dose of thyroid hormone used, despite the risk of developing thyroid hormone abnormalities has been reported in patients previously treated with interferon: however, endpoint data not statistically significant. Four patients had thyroiditis (3 had antithyroid antibodies) and 1 patient had hyperthyroidism before hypothyroidism. In 3 of these patients, spontaneous resolution of hypothyroidism was observed while hormone replacement therapy was required in one patient. Therefore, it can be concluded that nilotinib-induced thyroid dysfunction rarely requires clinical pharmacological treatment [31]. *Vandetanib*

Vandetanib is administered orally and has targeted activity at EGFR, VEGFR, and RET.

In a study with vandetanib administered at a dose of 100 mg/day in subjects with advanced hereditary medullary thyroid carcinoma who had previously undergone total thyroidectomy and all were on hormone replacement therapy, there was a mean 5.1-fold increase in serum TSH, but no cases of symptomatic hypothyroidism [32–34].

Mechanisms responsible for the induction of hypothyroidism

Understanding the mechanism leading to

Table 1. Examples of TKIs and their targets

Target	Drug	Approved indications
BCR-ABL	Imatinib Dasatinib Nilotinib	Chronic myeloid leukaemiaPhiladelphia chromosome positive acute lymphoid leukaemia
KIT	Imatinib Sunitinib	Gastrointestinal stromal tumour
PDGFR α/β	Imatinib	Chronic myelomonocyticleukaemia (with TEL-PDGFRâ fusion) Hypereosinophilic syndrome (with PDGFRâ fusion) Dermatofibrosarcoma protuberans
HER 2	Lapatinib	Her2+ breast cancer
EGFR	Gefitinib	Lung adenocarcinoma (with EGFR mutation)
VEGFR	SorafenibSunitinib	Kidney cancerHepatocellular carcinoma (sorafenib only)

hypothyroidism is a burning problem for scientists, they are conducting many different studies to answer this question. At present, there are no conclusive data, but various hypotheses have been proposed that need to be confirmed. Since this side effect was mainly observed with sunitinib use, many studies have focused on this TKI.

For sunitinib, multiple mechanisms appear to be involved:

1. Sunitinib appears to have a direct cytotoxic effect on thyroid cells, possibly by inhibiting the activity of VEGFR and/or PDGFR in thyroid follicular cells whose activity is only partially regulated by TSH [6,35,36.] Experiments in rats reported that administration of VEGF inhibitors induced capillary depletion in various organs, including the thyroid gland where the greatest regression (68%) was observed. . Other interesting data show that TSH can be increased up to 19 times than the control value, while free T4 is unchanged. It should be noted that after treatment with VEGF inhibitors, capillary remodeling occurs in thyroid tissue [37].

2. It appears that sunitinib leads to altered thyroid activity by the inhibitory action of the thyroid peroxidase (TPO) by blocking thyroid hormone synthesis. As the thyroid has reserves of thyroid hormones, this could explain the latency period between the start of sunitinib therapy and the development of hypothyroidism. The ability of sunitinib to inhibit TPO activity has been evaluated *in vitro* but not *in vivo* [38,39].

3. Sunitinib can block the absorption of iodine and thereby cause transient hypothyroidism. The most widely accepted mechanism for this effect proposes that sunitinib interacts with the iodine-sodium synchronizer (NIS), whose TSH regulation occurs via cAMP, unaffected by the drug. However, Sunitib does not seem to affect NIS [6].

4. Finally, sunitinib does not appear to induce autoimmune thyroid disease, as may occur with interferon-á and interleukin-based therapies [6]. As for sorafenib, it also inhibits VEGFR and PDGFR, thereby weakening the capillaries of thyroid tissue, but unlike sunitinib, it appears to interact with TSH-mediated regulation, because TSH is involved in RAF, which is a target of sorafenib. However, the potential effects of sunitinib on normal thyroid function have not been thoroughly investigated, nor can sorafenib have less of a thyroid effect than sunitinib [6,40].

DISCUSSION

Over the past 50 years, cancer treatment has evolved from the use of a highly toxic drug such as nitrogen mustard (classic cytotoxic, acting on all cells and having an extremely limited margin of selectivity) until recent years when certain drugs have been introduced to have hormonal regulatory effects on tumor growth or the cell cycle control mechanism underlying malignancies [41-44]. These new drugs belong to targeted molecular therapy that disrupt specific cell life signaling pathways and are more tolerable than traditional cancer drugs (Figure 1)[45,46].

Molecularly targeted therapeutic drugs designed to act on specific cellular targets that interfere with cell growth; this leads to a decrease in nonspecific toxicity. Molecular targeted therapy indeed exhibits lower toxicity than traditional therapies, but this should not be underestimated, as it can affect different areas of the body such as the cardiovascular, skin, lungs, liver, kidneys, thyroid, gastrointestinal tract and nerves [47 -50]. Side effects are usually of low intensity and are therefore more easily tolerated by patients; however, there may be degrees of toxicity that must be addressed by discontinuation of therapy or other pharmacological strategies. A distinction can also be made between targeted and untargeted side effects. Targeted toxicity is due to the primary pharmacological action of the drug (thus related to the drug's mechanism of action) while off-target toxicity is due to a secondary pharmacological effect of the drug (which is not related to the drug's mechanism of action)[3].

The most common endocrine disturbance associated with TKI use is hypothyroidism, which may develop ex-novo or, if pre-existing, requires an adjustment in the thyroxine dose. Although TKI-induced hypothyroidism is only a manageable side effect, some results suggest a potential prognostic role in cancer treatment efficacy. For example, in a study with sunitinib or sorafenib in patients with metastatic CRC, the clinical picture of hypothyroidism was found in 21 out of 66 patients (38.1%) and was associated with a better chance of survival (16.0 ± 0.8 months

versus 6.0±0.8 months, p=0.032)[51]. An explanation for the association between hypothyroidism and increased chances of survival after TKI treatment may be due to the inhibitory effect of hypothyroidism on tumor growth. The proposed mechanism suggests that thyroid hormone may stimulate the growth of certain types of tumors by acting directly or indirectly by regulating the expression of certain growth factors [6]. Clinical data show how hypothyroidism can inhibit tumor growth: in breast cancer patients, hypothyroidism is favorably associated with a lower risk of tumor development, less aggressive tumor, and advanced age [6,52].

Since data have suggested that the presence of hypothyroidism due to TKIs is associated with improved treatment efficacy, treatment of hypothyroidism may lead to worsening clinical outcomes [53-57]. Indeed, thyroid hormone replacement therapy may be permitted in patients with cancer who are active or in remission. However, elevated serum VEGF values have been identified in most hypothyroid patients receiving hormone replacement therapy [58–62]. It should be noted that some studies have failed to show a life expectancy benefit related to the development of hypothyroidism [6,63-65].

There are currently no recommendations for monitoring thyroid activity during treatment with TKIs and the interval for periodic measurement of TSH levels has not been determined. There are various suggestions, such as measuring thyroid function on the first day of each treatment cycle. However, it is certainly necessary to monitor thyroid function even after the end of TKI therapy to check its recovery [66-74]. A reasonable approach is to monitor thyroid function, both before and for 2-4 weeks after the end of treatment. If elevated TSH values are found shortly after stopping treatment, hypothyroidism is likely to persist and should be treated with thyroxine, as it may worsen in subsequent cycles of treatment. However, at present, further evaluation of the progression of thyroid function in TKI-treated patients is still needed to determine appropriate therapeutic measures [73-76].

CONCLUSIONS

The use of molecularly targeted drugs in therapy has resulted in improvements in the fight against cancer, as the therapeutic effect is more selective and the incidence of adverse events and toxicity is smaller than in the past. Furthermore, these effects are usually dose dependent and reversible. However, early symptoms of toxicity due to molecularly targeted therapies are often unrecognized by patients and not reported to oncologists. These first symptoms can develop into situations that are very dangerous and risky for the patient's health, and in some (rare) cases even lead to the death of the patient.

Therefore, patients should be monitored by the treating physician and properly informed about possible toxic effects so that they can be treated consciously and can be reported to the physician during the clinical examination.

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Conflict of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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