REVIEW

Tyrosine kinase inhibitors and modifications of thyroid function tests: a review

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Abstract

Tyrosine kinase inhibitors (TKI) belong to new molecular multi-targeted therapies that are approved for the treatment of haematological and solid tumours. They interact with a large variety of protein tyrosine kinases involved in oncogenesis. In 2005, the first case of hypothyroidism was described and since then, some data have been published and have confirmed that TKI can affect the thyroid function tests (TFT). This review analyses the present clinical and fundamental findings about the effects of TKI on the thyroid function. Various hypotheses have been proposed to explain the effect of TKI on the thyroid function but those are mainly based on clinical observations. Moreover, it appears that TKI could alter the thyroid hormone regulation by mechanisms that are specific to each molecule. The present propositions for the management of TKI-induced hypothyroidism suggest that we assess the TFT of the patients regularly before and during the treatment by TKI. Thus, a better approach of patients with TKI-induced hypothyroidism could improve their quality of life.

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Introduction

Protein tyrosine kinases (TK) are enzymatic proteins, usually receptors, which catalyse the transfer of phosphate from ATP to tyrosine residues in peptides. They are involved in the oncogenesis through various mechanisms, as described in a recent review (1): (i) a constitutively active fusion protein, created by a TK linked to a partner protein (BCR–ABL), (ii) a mutation or deletion of the kinase domain of the receptor altering its autoregulation or the sensitivity to its ligand (CSF1R-like tyrosine kinase 3, stem cell factor receptor, KIT), (iii) an increased or aberrant expression of TK receptors (platelet-derived growth factor receptor α , PDGFRA) or of their ligand, and (iv) a decrease in factors regulating TK activity (protein tyrosine phosphatases). Excessive activation of TK is involved in survival, proliferation, invasiveness and angiogenesis of the tumours (1).

The development of pharmacological tyrosine kinase inhibitors (TKI) is relatively recent. These new therapies belong to molecular targeted therapies. They block the tyrosine kinase signalling pathways that modulate, directly or indirectly, oncogenesis (2). Even if TKI are not specific of only one TK receptor, the majority exhibit vascular and anti-angiogenic properties by interacting with vascular endothelial growth factor (VEGF), VEGF receptors (VEGFRs) and PDGFR (2). Other targets of TKI such as RET and KIT are involved in the tumoral

growth. By targeting several TK receptors, the TKI can potentially interfere with different signalling pathways implicated in oncogenesis. Since 2005, many authors have reported changes of thyroid function tests (TFT) among patients with different TKI. In this review, we analyse the effects of four molecules: sunitinib, imatinib, motesanib and sorafenib. Indeed, only these molecules have been associated with thyroid test abnormalities until now.

Sunitinib

Clinical data

Sunitinib is presently approved for the treatment of advanced or metastatic renal cell carcinoma (RCC) and gastrointestinal stromal tumour (GIST) (3, 4). Sunitinib targets the VEGFRs, the PDGFRs, KIT and glial cell-line-derived neurotrophic factor receptor (RET) (3). All these TK receptors are involved in the tumour growth, angiogenesis, and metastatic potential, which are theoretical targets of sunitinib. The administration includes repeated 6-week cycles with 4 weeks of treatment (ON period) followed by 2 weeks without treatment (OFF period).

Several clinical studies have analysed the changes of TFT in patients treated with sunitinib (Table 1). In 2006, Desai *et al.* reported the first observations of

Table 1 Frequency of hypothyroidism during tyrosine kinase inhibitors therapies (sunitinib, imatinib, motesanib and sorafenib).

	Drugs	Subjects (n)	Indications	Hypothyroidism (%)
Desai (2006) (5)	Sunitinib	42	GIST	36
Mannavola (2007) (6)	Sunitinib	24	GIST	71
Rini (2007) (7)	Sunitinib	66	RCC	85
Wong (2007) (8)	Sunitinib	40	Solid (in majority GIST)	53
Chu (2007) (9)	Sunitinib	36	GIST	14
Wolter (2008) (10)	Sunitinib	59	RCC, GIST	61
De Groot (2005) (22)	Imatinib	11	MTC, GIST	100 in athyreotic subjects
De Groot (2007) (23)	Imatinib	15	MTC	100 in athyreotic subjects
Sherman (2008) (27)	Motesanib	93	DTC	22
Tamaskar (2007) (35)	Sorafenib	39	RCC	18

GIST, gastrointestinal stromal tumour; RCC, renal cell carcinoma; MTC, medullary thyroid carcinoma; DTC, differentiated thyroid carcinoma.

thyroid dysfunction (5). Among 42 euthyroid subjects treated by sunitinib for GIST, 62% had an abnormal TSH level: 36% had a persistent hypothyroidism with TSH > 7 mU/l and required levothyroxine replacement, 17% had a TSH concentration between 5 and 7 mU/l, and 10% had a TSH suppression. Since 2006, many authors have reported that sunitinib therapy is associated with hypothyroidism in 14–85% of the patients. In the study by Mannavola *et al.* 46% of patients developed hypothyroidism requiring levothyroxine therapy and 25% had a transient elevation of TSH (6). Rini *et al.* showed that TFT abnormalities were consistent with hypothyroidism in 85% of the 66 subjects treated for metastatic RCC (7). Even though some patients really had an increase in their TSH level, they preferentially had a decrease in their free triiodothyronine (fT₃) level rather than their free thyroxine (fT₄) concentration. Wong *et al.* analysed the effect of sunitinib in 40 patients with different solid tumours, including mainly GIST (8). After 5 months, sunitinib caused hypothyroidism in 53% of patients. However, the baseline thyroid function was unknown and 18% of patients with high TSH levels had a history of hypothyroidism. In a phase I/II trial focusing on the cardiotoxicity of sunitinib for GIST therapy, Chu *et al.* found 14% of hypothyroidism defined by high TSH values (9). On average, hypothyroidism appeared after 54 weeks. The latest published study prospectively analysed the effects of sunitinib among 59 patients with resistant RCC or with GIST (10). Its design appears to be the best of all designs in the aforementioned studies since TFT were performed before sunitinib was administered, as well as in the first and last days of each ON period. Sixty-one per cent of subjects were found to have a transient or permanent elevated TSH, and 27% of them required hormone replacement (10).

It is difficult to establish whether sunitinib-related hypothyroidism can be symptomatic. Indeed, hypothyroidism symptoms like asthenia, anorexia or cold intolerance are not specific, but are frequent in patients with cancer. Nevertheless, symptoms compatible with hypothyroidism have been described for most patients with high TSH (7, 10). Moreover, levothyroxine reduced symptoms in 50% of treated patients (7, 10).

The probability of hypothyroidism increases with time and each cycle of treatment (5, 6, 10). In all reported series, TSH concentration increased at the end of the ON phase and was near the normal range at the end of the OFF phase, leading to intermittent hypothyroidism. After several treatment cycles, baseline TSH levels seemed to increase, revealing a permanent hypothyroidism. Thus, an ongoing therapy increases the risk of developing hypothyroidism (10). Figure 1 shows the variations of TSH levels in a patient during sunitinib therapy for metastatic renal carcinoma (Dr Damate-Fauchery, personal data). The correction of TFT after definitive withdrawal of sunitinib is uncertain as the findings are conflicting (5, 6).

Physiopathological hypotheses

The mechanisms of alteration of TFT during sunitinib therapy are still unclear. After the publication of Desai *et al.* sunitinib-induced destructive thyroiditis was advocated (5). Indeed, in 40% of hypothyroid patients, thyroid abnormalities had a biphasic evolution with a decrease in TSH, which could correspond to a thyrotoxicosis status followed by an increase in TSH. Furthermore, in two subjects, no thyroid gland could be

Figure 1 Serum TSH fluctuating concentrations during sunitinib therapy in a patient with advanced renal cell carcinoma. Grey areas indicate the ON period (with drug administration) and white areas the OFF period (without drug administration). Striped area corresponds to the TSH normal range (0.35–4.5 mU/l). With permission from Dr Damatte-Fauchery, personal data.

identified by ultrasound. Recently, this thyrotoxicosis period preceding hypothyroidism has been reported during the first cycles of therapy (10–12). Grossmann *et al.* reported hyperthyroidism in 25% of patients with sunitinib for RCC (12). In two subjects, thyrotoxicosis was severe. The increased thyroglobulin level, the decreased iodine uptake, the progression to hypothyroidism and the presence of lymphocytic thyroiditis on fine needle aspiration reinforced the diagnosis of destructive thyroiditis (12). However, available data remain insufficient to assume that all sunitinib-induced hypothyroidisms are secondary to thyroid destruction.

Some works mention the anti-angiogenic effects of sunitinib. The inhibition of signal transduction cascade of VEGF by low molecular weight inhibitors of VEGF receptor (VEGFR) or by soluble VEGFR seems to be responsible for a capillary regression (13, 14). VEGF and VEGFRs are expressed by thyroid follicular cells and are, partly, regulated by TSH (15–18). In mice, the inhibition of VEGFR leads to a 68% reversible reduction in thyroid vasculature and the mouse hormonal phenotype corresponds to a primary hypothyroidism (13). As sunitinib targets VEGFRs, it can be hypothesized that the regression of thyroid capillary accounts for the destruction of follicular cells. Thus, by blocking VEGF signalling, sunitinib could damage the thyroid structure and change the thyroid function.

Following the study by Desai *et al.* other physiopathological hypotheses have been proposed. An iodine uptake inhibition could result in hypothyroidism (6). The majority of patients have a significant reduction of iodine uptake during the ON period of sunitinib therapy and this reduction is rapidly reversible during the OFF periods. Iodine uptake blocking could be involved in sunitinib-induced hypothyroidism, as there is a negative relationship between iodine uptake and TSH concentration. Moreover, the TSH level fluctuates according to the ON or OFF periods. However, until now, no effect of sunitinib on iodine uptake or on sodium iodide symporter (SLC5A5) has been demonstrated. An *in vitro* study even demonstrates the contrary (19). In FRTL-5 rat thyroid cells, sunitinib inhibited the cellular growth and increased the iodine uptake induced by TSH or forskolin. This dose-related effect did not appear to be mediated by SLC5A5 as there was no modification of *Slc5a5* mRNA expression. The iodine efflux was not affected either. Wong *et al.* reported an important inhibition of peroxidase activity (8). Sunitinib anti-peroxidase potency could be 25–30% of that of propylthiouracil. This effect could explain the latent period between the initiation of sunitinib and the development of hypothyroidism. Thus, hypothyroidism could appear only after the release of thyroid hormone reserve of the gland. Further research is still required because the links between peroxidase activity and TSH levels have not yet been evaluated. Data regarding the sunitinib-induced alterations of immune response are missing. Only about 4–10% of treated subjects seem

to develop thyroglobulin auto-antibodies (7, 10). In contrast with the interferon therapies, immunity does not appear to participate in the thyroid dysfunction (20). Impairment of iodine organification and reduced iodine uptake could play a role in the risk of hypothyroidism during sunitinib treatment, but those mechanisms cannot explain the thyrotoxicosis period before hypothyroidism. This is the reason why the hypothesis of destructive thyroiditis seems to be the predominant effect of sunitinib-related hypothyroidism.

Imatinib

Clinical data

Imatinib is primarily approved for the treatment of Philadelphia chromosome (BCR–ABL) positive chronic myeloid leukaemia in blast crisis, accelerated phase or in chronic phase and of Kit-positive GIST (21). Imatinib is a multi-targeted TKI that interacts with BCR–ABL, non-receptor fusion tyrosine kinase, PDGFR and KIT (2).

Imatinib-induced modifications of the thyroid function have been studied by de Groot *et al.* In 2005, de Groot *et al.* reported hypothyroidism frequency among ten imatinib-treated patients for medullary thyroid carcinoma (MTC) (22). Seven of them had undergone thyroid surgery. One patient was treated for GIST. Only the seven athyreotic patients (and not the patients with thyroid *in situ*) had an increased TSH concentration, which approached five times the upper normal value. Hypothyroidism remained subclinical as, even if ft_4 and ft_3 levels were reduced by 59 and 63% respectively, they remained within the normal range. The same group assessed the effect of imatinib among 15 subjects with metastatic MTC (23). In the same way, TSH changes were present only in athyreotic subjects. The ft_4 and ft_3 values were not reported, but there was a 210% increase in the levothyroxine replacement dose. This effect appears rapidly after an initiation of therapy and is reversible, since TSH normalized after discontinuation of imatinib (22). Even if it seems that imatinib therapy does not alter the thyroid function, results must be interpreted with caution, considering the low number of subjects in those two studies.

Physiopathological hypotheses

The studies quoted above cannot clearly identify an action of imatinib on the thyroid gland (22, 23). The majority of patients treated have indeed undergone thyroidectomy and the absence of effects of imatinib on patients with thyroid *in situ* does not suggest a veritable action on thyroid tissue itself. Lately, Dora *et al.* confirmed these results, as they showed that imatinib did not induce any modifications of the thyroid hormonal status in 68 patients with thyroid *in situ* treated for chronic myeloid leukaemia (24). Imatinib could interfere with T_4 metabolism and not with thyroid

hormonal synthesis. The absorption of levothyroxine did not seem to be impaired by imatinib, since the separate administration of the two medications did not modify TSH levels (22). The absence of changes in thyroxine-binding globulin and total thyroxine levels neither supports competition for thyroid hormone-binding sites nor supports deiodinase inhibition (22). Thus, de Groot *et al.* suggest that imatinib could stimulate the T₄ and T₃ clearances by the induction of uridine diphosphate-glucuronosyltransferases (UGTs) (22, 25). However, potential interactions between UGTs and imatinib remain to be proven.

Motesanib (AMG 706)

Motesanib targets TK such as VEGFR, PDGFRs, KIT and RET (2). Today, motesanib is evaluated for second-line therapy in differentiated thyroid carcinoma (DTC), MTC and for other solid tumours (sarcoma, melanoma, lung, kidney, colon and GIST) (26–28).

The motesanib thyroid cancer study group evaluated the motesanib-induced thyroid function modifications in a phase II safety/efficacy study (26, 27). About 93 patients treated for a DTC and 91 for an MTC, all with levothyroxine substitution, were followed for an average of 100 days. During therapy, almost 50% of the patients showed a TSH concentration ten times higher than the baseline value on at least one occasion. Hypothyroidism or TSH above the reference range was present in 22% of DTC and 61% of MTC (26, 27). Thus, the levothyroxine replacement dosages had to be increased during motesanib therapy.

No published studies deal with the interactions between motesanib and thyroid gland function. Like imatinib, data are based on athyreotic patients. In this population, TFT changes suggest an indirect effect of motesanib similar to that of imatinib. However, thyroid anti-angiogenic action remains possible. In mice, motesanib inhibits the proliferation of endothelial cells and reduces vascular permeability induced by VEGF (29). In tumour xenografts, motesanib reduces tumour growth and induces tumour regression, which is preceded by a proapoptotic action on endothelial cells. Thus, the effects of motesanib could be double via action on the thyroid tissue and via action on the metabolism of thyroid hormones. A recent study on safety and tolerance of motesanib on solid tumours has not reported the alterations of TFT and only studies in patients with thyroid *in situ* could highlight the actions of motesanib on the thyroid (28).

Sorafenib (BAY 43-9006)

Sorafenib is also a multi-targeted TKI that interacts with VEGFRs, PDGFRB, KIT, RET, BRAF and RAF1 (2, 30). Sorafenib is approved for the treatment of advanced RCC

and unresectable hepatocellular carcinoma (31). It has been evaluated in lung, pancreatic, prostate cancers, melanoma and DTC (32–34).

Abnormalities in TFT have been reported in 39 euthyroid subjects treated by sorafenib for metastatic RCC (35). Two to four months after sorafenib initiation, 18% of subjects presented hypothyroidism, and one quarter of them developed thyroglobulin antibodies. Hypothyroidism would persist after sorafenib withdrawal. One patient (3%) exhibited hyperthyroidism but its baseline thyroid status was unknown. Thyroid tests compatible with non-thyroidal illness were described in 21% of cases.

Sorafenib inhibits VEGFR and PDGFRB signalling pathways and reduces angiogenesis in human tumour xenografts (30, 36). In orthotopic anaplastic thyroid carcinoma xenografts, sorafenib induces an endothelial apoptosis (37). This anti-angiogenic effect results in reduced tumour growth and improved survival of mice. Sorafenib also seems to decrease proliferation and survival of tumour cells by blocking the RAF/MEK/ERK pathway (30, 36). These combined actions can explain the anti-tumoral activity of sorafenib. Nevertheless, anti-proliferative activity was not explored on non-tumoral thyroid tissue. Sorafenib could also interact with TSH-signalling pathways. Indeed, the TSH signal transduction cascade has been reported to involve the RAF pathway, a target of sorafenib (38, 39). However, no study has analysed the effect of inhibition of this pathway on thyroid hormone synthesis. Such studies could provide a better understanding of sorafenib-induced hypothyroidism.

Management of thyroid function abnormalities during TKI therapy

TKI affect thyroid function through different physiopathological mechanisms that can impair the thyroid tissue or the thyroid hormone metabolism. Initiation of TKI therapy requires TFT monitoring before, and during, the first weeks of therapy in all patients with *in situ* thyroid and thyroidectomized patients. Considering available data, a monthly TSH assessment could be performed, as we do not possess a better knowledge of the effect of each TKI. Wolter *et al* proposed measuring TSH on day 1 and day 28 in the first four cycles of sunitinib treatment and then every three cycles if the preceding TSH were normal (10). Presently, other TKI are being evaluated (including vandetanib and dasatinib) and it would be judicious to assess their effect on thyroid function during phase II and III trials.

The question of thyroid hormone substitution in TKI-induced hypothyroidism has been raised recently following the publication of a report which concluded that the median progression-free survival in sunitinib-treated patients for renal carcinoma cell was better in patients with thyroid abnormalities (40–42). Even

though levothyroxine therapy remains debated in patients with asymptomatic or subclinical hypothyroidism, levothyroxine seems to be necessary in TKI-induced overt hypothyroidism in order to avoid the symptoms of hypothyroidism. Hormone replacement can be difficult during sunitinib therapy. Sunitinib therapy is indeed proposed in the cycles composed of a 4-week ON period followed by a 2-week OFF period. An elevated TSH level during the OFF period would definitely require levothyroxine substitution, whereas an increased TSH during the ON period could spontaneously return to normal in the OFF period. Thus, a hyperthyroidism might appear if levothyroxine substitution is introduced. That is why the OFF period TSH levels could be more informative than the ON period TSH levels when making hormone replacement decisions.

Conclusions

TKI are new molecular targeted therapies approved for the treatment of several haematological and solid tumours. Many studies clearly have demonstrated that TKI were able to induce disturbances of TFT. The indications of TKI will probably be broadened and will then increase the number of subjects with thyroid dysfunction. Oncologists and endocrinologists must become aware of TKI-induced TFT alterations so as to detect and treat them. Hopefully, a close collaboration between oncologists and endocrinologists should help to improve the quality of life of these patients.

Declaration of interest

All authors of this manuscript have no conflict of interest.

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