ENDOCRINE SIDE-EFFECTS OF ANTI-CANCER DRUGS

Thyroid effects of tyrosine kinase inhibitors

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Abstract

Tyrosine kinase inhibitors (TKIs) are currently used by most oncologists. Among their side effects, thyroid dysfunctions are nowadays clearly observed. Whereas changes in thyroid function tests have been originally described with sunitinib, we now know that many TKIs can induce hypothyroidism and hyperthyroidism. In this study, the various molecules implicated in thyroid dysfunctions are analysed and the latest data on physiopathological mechanisms are approached in order to propose a strategy of thyroid monitoring of patients on TKI therapy.

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Introduction

For the last 10 years tyrosine kinase inhibitors (TKIs) have been largely used as first- or second-line therapy of various solid tumours or haemopathies. They inhibit the transfer of phosphate from ATP to tyrosine residues in the catalytic domain of growth factor receptors. Their targets are involved in the survival, proliferation, invasiveness and angiogenesis of the tumours (1). The safety and tolerability are different and depend on the molecules, but thyroid effects of sunitinib were rapidly

observed (2, 3). Since 2006, changes in thyroid function tests (TFTs) have been reported with different TKIs in subjects with thyroid *in situ* and in thyroidectomised subjects (3, 4). In the first part of this review, we discuss the effects of TKI on TFT. In the second part, we focus on the mechanisms that are currently proposed to explain the changes on TFT. Finally, we endeavour to propose a strategy to monitor the TFT before, during and after the withdrawal of the TKI.

Invited Author's profile

Ulrich Schweizer studied biochemistry in Bayreuth, Germany, and received his PhD in neurobiology from the University of Würzburg. After more than ten years in the Neuroscience Research Center and in the Institute for Experimental Endocrinology at Charité-Universitätsmedizin Berlin, he moved to Bonn as a professor for biochemistry. He is interested in the biochemistry and physiology of selenoproteins in brain and thyroid, and in selenoprotein biosynthesis in general. Research on iodothyronine deiodinases brought him to the study of structure and function, as well as physiology, of thyroid hormone transporters. He is a member of the European Society of Endocrinology and the European Thyroid Association.

TKI-induced modification of thyroid status

Sunitinib

Among TKI-induced thyroid dysfunctions, sunitinib has been the most studied molecule (Table 1). In a phase I/II trial, Desai *et al.* (3) were the first to report TFT in 42

euthyroid subjects treated with sunitinib for imatinib-resistant gastrointestinal stromal tumours (GISTs). An abnormal TSH level was found in 62% of subjects, which corresponds to a TSH concentration >20 mU/l in 21%, >7 mU/l in 14%, between 5 and 7 mU/l in 17% and below the normal range (<0.5 mU/l) in 10%. Levothyroxine

Table 1 Frequency of hypothyroidism, of changes of thyroid function tests or of adjustment of thyroid hormone dose during TKI therapies.

Reference	Tyrosine kinase inhibitor	Subjects (n)	Tumoural indications	Hypothyroidism or other if indicated (%)
(3)	Sunitinib	42	GIST	36%
(6)	Sunitinib	24	GIST	71%
(7)	Sunitinib	40	Solid tumours (in majority GIST)	53%
(8)	Sunitinib	36	GIST	14%
(9)	Sunitinib	66	RCC	85%
(10)	Sunitinib	59	RCC, GIST	61%
(11)	Sunitinib	375	RCC	14%
(14)	Sunitinib	21	RCC	62%
	Sorafenib	21	RCC	38%
(15)	Sunitinib	86	PET	7%
(12)	Sunitinib	146: 6-week cycle 143: daily dose	RCC RCC	13% 8%
(5)	Sunitinib	102	RCC	50%
(13)	Sunitinib	548	RCC	24%
	Pazopanib	554	RCC	12%
(20)	Sorafenib	39	RCC	18%
(28)	Sorafenib	33	DTC	30%: adjustment of TH dose
(30)	Sorafenib	31	DTC	19%: increase of levothyroxine 16%: decrease of levothyroxine
(29)	Sorafenib	41	DTC	No adjustment of TH dose
(31)	Sorafenib	34	DTC, MTC	12%: raised TSH levels
(32)	Sorafenib	31	DTC	42%: adjustment of TH dose
(22)	Sorafenib	355	RCC	8%: hypothyroidism
(23)				14%: start or increase of levothyroxine
	Axitinib	359	RCC	20%: hypothyroidism
				27%: start or increase of levothyroxine
(21)	Sorafenib	28	RCC	29%: hypothyroidism or increase of TH dose
	Sunitinib	45	RCC	51%: hypothyroidism or increase of TH dose
(24)	Sorafenib	1295	Unknown	6% start of TH
	Sunitinib	1214		14% start of TH
(35)	Vandetanib	17	MTC	100%: raised TSH levels
(33)	Vandetanib vs placebo	231 vs 99	MTC	49%: increase of levothyroxine
(40)	Motesanib	93	DTC	22%
(41)	Motesanib	91	MTC	42%
(42)	Cabozantinib vs placebo	241 vs 109	MTC	59%: raised TSH levels above the normal range
(43)	Cabozantinib	171	Prostate cancer	15%
(44)	Pazopanib	37	DTC	62%: increased TSH by more than two times
(45)	Nilotinib	55	CML	22%
	Dasatinib	10	CML	50%
(4)	Imatinib	11	MTC, GIST	100% (athyreotic subjects)
(49)	Imatinib	15	MTC	100% (athyreotic subjects)
(50)	Imatinib	68	CML	0% (nonthyroidectomised subjects)
(51)	Axitinib	6	RCC	100%

GIST, gastrointestinal stromal tumour; RCC, renal cell carcinoma; pNET, pancreatic endocrine tumour; MTC, medullary thyroid carcinoma; DTC, differentiated thyroid carcinoma; CML, chronic myeloid leukaemia; TH, thyroid hormone.

(L-T₄) therapy was started in some patients. Among the patients developing hypothyroidism, 40% first had a suppressed TSH concentration followed by hypothyroidism. Since this study, physicians have been interested in sunitinib-induced thyroid changes and have analysed the TFT. In clinical trials, the incidence of thyroid dysfunction varies between 7 and 85% (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15). Among 102 patients with normal TFT on baseline, 50% developed hypothyroidism (5). The recognition of this hypothyroidism was clinically relevant as 91% of patients received L-T₄ therapy. Motzer *et al.* (11, 13) studied the efficiency of sunitinib and pazopanib on renal cell carcinoma (RCC). The phase III trials are the two largest trials allowing to analyse the effect of these molecules on TFT (11, 13). One study included 375 patients treated with either sunitinib or interferon- α . Hypothyroidism appeared in 14% of patients on sunitinib and 2% on interferon- α (11). In the other study, 554 and 548 patients were assigned to either sunitinib or pazopanib (13). Hypothyroidism was present in 24 and 12% in the sunitinib and pazopanib groups respectively. Whereas a phase of hyperthyroidism preceding hypothyroidism was described in several trials, this was not reported in the two studies of Motzer *et al.* (3, 6, 10, 11, 12, 13, 14, 15, 16). Furthermore, isolated hyperthyroidism without secondary hypothyroidism has never been reported.

Several authors have reported that the risk of developing hypothyroidism increases with time and with the number of cycles of sunitinib therapy (3, 6, 10). Sunitinib is usually given in repeated 6-week cycles with a 4-week ON period followed by a 2-week OFF period. The classical feature of TFT alteration depends on the number of cycles (3, 6). Indeed, the TSH level increases during the ON period and decreases during the OFF period. It is noteworthy that with the repeated cycles of treatment, the TSH level gradually increases and can remain elevated at the end of the OFF period (Fig. 1). Thus, the TSH level can be slightly elevated when the patient resumes a new cycle of therapy. In the two largest series with a long follow-up, the median time to hypothyroidism onset seems extremely variable and can appear as late as 94 weeks after the start of sunitinib (3, 10, 11, 13). In patients with normal TFT, no baseline thyroid parameter has been described that could predict a developing hypothyroidism (3, 10). The long-term cumulative incidence of hypothyroidism is unknown.

Sunitinib is effective in treating metastatic pancreatic neuroendocrine tumours but at a lower dose and in continuous daily administration (37.5 mg/day), compared with placebo (15). Among 86 patients on sunitinib, six

developed hypothyroidism with no hyperthyroidism, which is less than the incidence of hypothyroidism in the studies with cycle pattern. There is no explanation for this lower incidence of hypothyroidism, but the lower dose of sunitinib. Even though oncologists are nowadays aware of sunitinib-induced hypothyroidism, severe hypothyroidism and myxoedema have been reported (17, 18, 19). These cases raised some questions about the physiopathological mechanisms of sunitinib-induced hypothyroidism. Although the T₄ level was very low or undetectable, the TSH level was not as elevated as expected. It cannot be excluded that sunitinib negatively affected the hypothalamic or pituitary thyrotropic function.

The outcome of hypothyroidism after the withdrawal of sunitinib is currently unclear as some patients remain in hypothyroidism and others recover a normal thyroid function (3, 6).

Figure 1

Variations of TSH concentrations during sunitinib therapy. (A) The patient was treated with sunitinib for a differentiated thyroid carcinoma, and no levothyroxine adjustment was necessary. (B) The patient was treated with sunitinib for a medullary thyroid carcinoma but the fluctuations of TSH level required several changes of levothyroxine dose. Grey areas indicate the ON period (with sunitinib) and white areas the OFF period (without sunitinib). On the top, levothyroxine dose (μ g/day) is mentioned. TSH, closed triangle; FT₄, closed diamond.

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Sorafenib

The first thyroid dysfunction due to sorafenib was reported by Tamaskar *et al.* (20). Among 39 patients treated for RCC, 18% had a mild elevated TSH level (up to 10 mU/l) and 3% had a high TSH level (up to 160 mU/l). Six percent of patients had thyroglobulin antibodies. In this cohort, 3% of patients had hyperthyroidism 6 weeks after the introduction of sorafenib and 21% had a TFT compatible with a nonthyroidal illness. In Clemons' study, thyroid test abnormalities were retrospectively analysed in patients on sunitinib and sorafenib for RCC (21). On sorafenib, hypothyroidism appeared in six of 22 (27%) initially euthyroid subjects. Moreover, in two of six (33%) hypothyroid subjects at baseline, the dose of thyroid hormone had to be increased. In sunitinib-treated patients, hypothyroidism was more frequent and reached 44%. The same frequency of TFT modifications was reported in the randomised phase III trial AXIS, which compared the efficacy of axitinib and sorafenib therapy for RCC in 714 patients (22, 23). Hypothyroidism appeared in 8% of sorafenib-treated patients and thyroid replacement had to be started or increased in 14%. In a large retrospective German cohort database, 6.3% patients on sorafenib received a prescription of thyroid hormone (24). The incidence was higher on sunitinib as 178 of 1295 patients (13.7%) had begun thyroid hormone replacement, which corresponds to an incidence rate of 24.2 per 100 person-years. These different frequencies were reported in other studies also (14, 21).

Sorafenib-induced hyperthyroidism was reported in several studies or case reports (20, 25, 26). Hyperthyroidism was followed by a phase of hypothyroidism, and the ultrasonographic and scintigraphic evaluations were in favour of destructive thyroiditis. A fatal sorafenib-induced thyroid storm was even reported although the pretreatment thyroid function was unknown (27). No hyperthyroidism was mentioned in the largest prospective trial (22, 23). Nevertheless, antithyroid drugs were prescribed in 3.1% of patients on sorafenib in the German cohort study (24). However, no information concerning these patients was specified (24). The frequency of this prescription was similar to that in sunitinib-treated patients (24).

Sorafenib was also evaluated in patients with differentiated or medullary thyroid cancer and, therefore, in patients without a thyroid gland (28, 29, 30, 31, 32). In four of the five trials, an increase in thyroid hormone requirement was observed. An elevated TSH level was observed in 12 and 33% of patients in the studies of Ahmed *et al.* (31) and Gupta-Abramson *et al.* (28)

respectively. Changes of L-T₄ dose were performed in 42% of patients with sorafenib in the study by Schneider *et al.* without precisely informing whether it was an increase or a decrease of the dose (32). In another trial, an increase in the daily dose was necessary in 19% and a reduction in 16% of patients (30). It can be hypothesised that the dose adjustment was due to interference between sorafenib and L-T₄ absorption and metabolism. The reduction of L-T₄ could be due to the anorexia and weight loss, which are frequent with TKI molecules. A nonthyroidal illness could also exist and lead to these changes.

The median time to develop hypothyroidism was 20 months, but an increase of TSH could appear as early as 6 weeks after initiation of treatment (20, 21). Few data exist on the recuperation of normal thyroid hormone equilibrium after the withdrawal of sorafenib. Some patients recovered a euthyroid status so that no conclusion on the long-term outcome of sorafenib-related hypothyroidism can be drawn (20, 21, 25).

Vandetanib

Vandetanib is currently approved for the treatment of metastatic medullary thyroid carcinoma (MTC) and has been evaluated in metastatic radioiodine-refractory differentiated thyroid carcinoma (DTC). In the phase II trial conducted by Wells *et al.* (33) in 330 patients with advanced or metastatic MTC, a rise of TSH was described in 49.3 and 17.2% of patients with vandetanib and placebo respectively. As most patients are supposed to be thyroidectomised, this elevated TSH level is probably related to a modification of the metabolism of L-T₄ or to an interference with TSH metabolism or the pituitary or hypothalamic feedback loop (34). An increase of TSH was also observed in 17 athyreotic patients with advanced or metastatic MTC with a mean and median increase of 5.1- and 7.3-fold the baseline level (35). An ancillary study of two phase-randomised trials was specifically dedicated to assessment of endocrine dysfunctions induced by vandetanib (36). In 35 patients on vandetanib, 74% needed an increase of L-T₄ dose to maintain the targeted TSH level. The median increase corresponded to 50% of the baseline L-T₄ dose. It is noteworthy that TSH did not change in three nonthyroidectomised subjects which suggests, though not demonstrates, that vandetanib does not act on the thyroid gland itself. Unfortunately, in large trials evaluating the efficiency of vandetanib in non-small-cell lung cancer, no information was available about the TFT (37, 38, 39).

Motesanib

A phase II trial with motesanib in patients with progressive radioiodine-refractory DTC was published in 2008, but no phase III trial was conducted (40). Among 93 patients, an increased TSH level and/or a hypothyroidism was reported in 22%. A parallel phase II trial for patients with progressive or symptomatic MTC was published in 2009. Among 91 patients, 41% had a hypothyroidism and/or elevated TSH level during the follow-up (41). No data exist about thyroid effects of motesanib on nonthyroidectomised subjects.

Cabozantinib

Cabozantinib is a more recent TKI that has just been approved for metastatic progressive MTC (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203756lbl.pdf). In a phase III trial, cabozantinib induced a rise of TSH level in 57% of subjects compared with 19% of placebo group subjects (42). In our experience, the variations of the TSH level were frequent and upwards as well as downwards adjustments of L-T₄ were necessary. Appreciating the causes of these changes of dose is difficult. The anorexia, dysgeusia and diarrhoea are very frequent and the induced weight loss can itself participate in the reduction of the L-T₄ dose. In a phase II trial in patients with advanced prostate cancer, hypothyroidism was found in 15% (43). Although there was no indication on thyroid hormone treatment preceding enrolment, we can assume that these patients had not been thyroidectomised. Cabozantinib seems, therefore, to induce changes of TFT in all subjects.

Pazopanib

Motzer *et al.* (13) reported hypothyroidism in 12% of patients on pazopanib for a RCC. In a small study of 37 patients treated with pazopanib for a radioiodine-refractory metastatic differentiated thyroid cancer, the TSH level increased by more than twofold during treatment in 62% (44). In the other trials evaluating pazopanib, no thyroid status data were provided.

Nilotinib

Nilotinib was evaluated in 55 patients with Philadelphia chromosome-positive chronic myeloid leukaemia (CML) included in several trials (45, 46, 47). Hypothyroidism and hyperthyroidism phases were recorded in 22 and 33% of

patients respectively. However, 13% had a thyroid dysfunction before the start of nilotinib and 7% had thyroid antibodies during treatment. A phase of hyperthyroidism preceding hypothyroidism was present in 22% of patients, which could correspond to a destructive thyroiditis. A clinical hypothyroidism with oedema on nilotinib was also reported; this oedema had regressed with L-T₄ (48).

Imatinib

There are limited data on TFT during imatinib treatment, most coming from de Groot's group (4, 45, 49). In a phase II trial, 15 patients with metastatic MTC were treated with imatinib and thyroid hormone dose had to be increased in nine patients (60%), who were all athyreotic. The nonthyroidectomised patients always kept a normal thyroid function. This was confirmed in another trial with thyroidectomised and nonthyroidectomised patients and in a short report from Brazil, where no thyroid dysfunction was found in 68 nonthyroidectomised patients on imatinib (4, 50). This argues against a direct thyroid effect of imatinib. Kim *et al.* (45, 46) report on TFT changes observed in CML patients treated with imatinib, while the original study did not comment on altered TFT.

Axitinib

In the phase III trial AXIS, 20% of patients on axitinib for RCC were found hypothyroid, and 27% either started or increased their thyroid hormone dose (22, 23). The thyroid effect of axitinib was also demonstrated by the fact that among patients with baseline TSH level lower than 5 mU/l, one-third had a TSH elevation above 10 mU/l during their treatment. Among six patients treated for RCC, hypothyroidism or hyperthyroidism was also reported in all six patients. In five patients, hyperthyroidism was the first manifestation, suggesting a destructive thyroiditis (51).

Dasatinib

Dasatinib was initially used as a second-line TKI for imatinib-resistant CML and later approved as a first-line treatment. Out of ten patients treated with dasatinib, five had hypothyroidism and two had hyperthyroidism (45). Hypothyroidism was never preceded by a phase of hyperthyroidism (45).

Mechanisms that are currently proposed to explain the changes of TFT

Many different mechanisms have been proposed as to how TKI impacts the HPT axis. These can be grouped according to the proposed action on: i) thyroid gland integrity and thyroid hormone biosynthesis; ii) thyroid hormone transport; iii) thyroid hormone metabolism; and iv) pituitary TSH.

Thyroid gland integrity and thyroid hormone biosynthesis

Direct involution of the thyroid or thyroid autoimmunity is frequently found among patients treated with sunitinib, sorafenib and nilotinib, but not imatinib (3, 20, 45). The frequent hyperthyroidism followed by hypothyroidism may serve as an indication of destructive processes in the thyroid gland. One possible mechanism is capillary dysfunction due to inhibition of VEGF receptors (52, 53, 54). Fenestrated capillaries remain VEGF dependent after development and the thyroid was the organ in which capillary regression was greatest in mice treated with axitinib or soluble VEGFR (55). Capillary dysfunction may be followed or paralleled by direct destruction of the gland with or without the development of thyroid autoantibodies. Autoimmune thyroiditis may contribute to further damage of the thyroid. The persistence of hypothyroidism after the end of treatment may be a sign of irreversible thyroid tissue damage. Negative effects on thyroid hormone biosynthesis were suggested by inhibition of iodine uptake or inhibition of thyroperoxidase activity (6, 7).

Thyroid hormone transport

We have recently shown that increased L-T₄ requirement could be caused by impaired thyroid hormone transmembrane transport (56). Thyroid hormones are amino acid derivatives and as such require transport proteins in order to cross lipid bilayers and reach their nuclear receptors. The most prominent thyroid hormone transport protein is monocarboxylate transporter 8 (MCT8), the mutation of which in humans leads to a syndrome of altered TFTs and severe psychomotor retardation (57). MCT8 is expressed in the thyroid, where it may serve as a thyroid hormone exporter, and in pituitary, neurons, brain capillaries, hepatocytes and kidney tubular epithelium, where it mediates thyroid hormone uptake. We have shown that MCT8 is inhibited by imatinib, sunitinib,

dasatinib and bosutinib at concentrations similar to plasma concentrations during treatment (56, 58). A close homologue of MCT8 is MCT10, a thyroid hormone transporter expressed in the muscle. Both molecules are inhibited by desipramine, and desipramine induces hypothyroidism in rat brain as judged by induction of type 2 deiodinase (59, 60). This finding and recent experiments in transgenic mice suggest that brain uptake of thyroid hormones is mediated to a significant extent by MCT8 (57).

At least for thyroidectomised patients on L-T₄ replacement therapy, thyroid hormone uptake along the gastrointestinal tract is also a potential mechanism that may be altered by TKI. If transporters like MCT8 are needed to import and export thyroid hormones across plasma membranes, it is conceivable that uptake of L-T₄ in the gut likewise requires transporters. These transporters have not yet been identified. They may be inhibited by TKI in a similar manner as MCT8.

Thyroid hormone metabolism

Sorafenib leads to decreased ratios of tri-iodothyronine (T₃)/T₄ and T₃/rT₃, a finding compatible with increased inactivation of thyroid hormones by enhanced type 3 deiodinase activity (61). However, deiodinase activity was not directly determined in patients. In a rat study, sunitinib induced type 3 deiodinase activity in the liver (52). In patients treated with sunitinib, the T₃/T₄ and T₃/rT₃ ratios decreased, similarly indicating enhanced

Figure 2

Proposition of thyroid function test evaluation during sunitinib therapy.

thyroid hormone metabolism (52). Induction of type 3 deiodinase is often seen in states of illness, but no molecular mechanism for how TKI might induce type 3 deiodinase has been presented. In a very recent report, Maynard *et al.* (62) described a severe hypothyroidism in a patient with GIST before starting treatment with sunitinib. They showed that hypothyroidism was due to marked overexpression and activity of type 3 deiodinase in the tumour. In the GIST-T1 cell line, sorafenib and sunitinib increased type 3 deiodinase activity and mRNA that could contribute to the development of hypothyroidism during TKI therapy (62).

TSH metabolism

An elevation of TSH is the usual response towards most TKI. It may be caused by a decrease of T_3 and/or T_4 , inhibition of pituitary MCT8 or a negative effect on pituitary capillaries. In athyroid patients treated with sorafenib, TSH clearance is reduced (34).

How to manage TKI-induced thyroid dysfunctions?

The prescription of TKI requires a thyroid hormonal evaluation before starting them, but it is also essential to continue to monitor the thyroid function during and after the end of treatment. The recommendations are based on the analyses of sunitinib-induced thyroid dysfunctions (10). The authors proposed an evaluation of the TSH concentration dosage on the first and last days of the ON period during the first four cycles. If the TSH is normal, the measurement should then be repeated every three cycles. In cycle pattern, it can be difficult to decide when the $L-T_4$ has to be introduced (Fig. 1). The increased TSH level at the end of the OFF period confirms that the hypothyroidism is permanent and that it will worsen during the following cycles. Thus, $L-T_4$ will have to be started. Conversely, the increased TSH level during the ON period can be normalised at the end of the OFF period, and introduction of $L-T_4$ may lead to thyrotoxicosis (Fig. 1). We propose to determine the TSH level at the end of the ON period and, if it is elevated, to reassess it at the end of the OFF period in order to decide whether $L-T_4$ must be introduced (Fig. 2). During sunitinib continuous daily administration, we recommend to test TSH levels every month, and this procedure should also be proposed for sorafenib, cabozantinib, nilotinib and pazopanib. On imatinib, only athyreotic patients will have to be monitored. The outcome of hypothyroidism after the withdrawal of TKI

is unclear (3, 6). Thus, we propose to test thyroid function 2–4 weeks after the end of treatment. However, only methodical analyses of TFT changes during phase II and III trials will allow to improve our diagnostic and therapeutic strategies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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