Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy

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Abstract | Despite their inherent selectivity, targeted therapies such as tyrosine kinase inhibitors (TKIs) can cause unusual adverse effects. Sunitinib and sorafenib are multitargeted TKIs that have been demonstrated to induce hypothyroidism and thyroid dysfunction. Retrospective studies indicate that sunitinib can induce hypothyroidism in 53–85% of patients, and in prospective studies this complication has been reported in 36–71% of patients. Sorafenib has been reported to be responsible for hypothyroidism in 18% of patients with metastatic renal-cell carcinoma. Furthermore, imatinib and sunitinib seem to increase the requirement of levothyroxine in hypothyroid patients. The management of thyroid dysfunction and possible related symptoms, such as fatigue, represents a challenge to oncologists. We propose a diagnostic and therapeutic algorithm for the management of TKI-related hypothyroidism. Prospective trials are needed to define the incidence of overt and subclinical hypothyroidism and thyroid dysfunction during therapy with sunitinib, sorafenib and potentially other TKIs. The safety and efficacy, and optimal dosing and timing of starting replacement therapy in patients affected by TKI-related hypothyroidism need accurate appraisal and should be evaluated prospectively in appropriately designed trials.

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Introduction

A number of targeted agents have demonstrated activity and efficacy in many cancer histotypes, both in combination with chemotherapy or radiotherapy, and as single agents. Owing to the inherent selectivity of targeted drugs, these agents are generally associated with a lower toxicity compared with conventional systemic cytotoxic drugs (Table 1). The introduction of targeted drugs in the clinic has resulted in unusual adverse effects, such as hypertension, gastrointestinal perforation, arterial thromboembolism, reversible posterior leukoencephalopathy, cardiotoxic effects, skin damage, hypertension and renal impairment. Although these adverse effects are rarely life-threatening, they can cause considerable physical and psychosocial discomfort, which might lead to decreased quality of life for patients, or the need to reduce or discontinue therapy.[1] Moreover, the cytostatic mechanisms of action of targeted therapies can require that they are administered for long periods to be effective; as a result, therefore, new long-term toxicities are emerging.

Thyroid dysfunction[2–7] is an uncommon adverse effect of chemotherapeutic anticancer treatments.[8–24] Some small-molecule tyrosine kinase inhibitors (TKIs) have been shown to cause hypothyroidism-related symptoms to a variable extent, which can reduce a patient's quality of life. We review the available data for TKI-related thyroid dysfunction and the hypothesized pathophysiological mechanisms of this toxicity.

Competing interests
The authors declared no competing interests.

Cancer therapy and thyroid dysfunction

Several different mechanisms exist by which anticancer treatments can alter normal thyroid function. Cytotoxic chemotherapy can alter hypothalamic, pituitary, or thyroid function in a small proportion of patients.[9] An increased incidence of primary hypothyroidism has been documented in patients treated with multiple drug regimens, with or without radiotherapy.[9] In patients with testicular cancer who received combinations of cisplatin, bleomycin, vinblastine, etoposide, and dactinomycin, 4 of 27 individuals (15%) developed primary hypothyroidism.[10] In particular, the cumulative doses of cisplatin and vincristine seem to exacerbate these symptoms.[10] In total, 44% of patients treated with MOPP regimen (mechlorethamine, vinblastine, procarbazine and prednisolone) for Hodgkin disease developed elevated serum thyroid stimulating hormone (TSH) concentrations, although a causative role of iodine load during lymphangiograpy cannot be excluded.[11]

Primary hypothyroidism might be caused by cytokine treatments. Interleukin-2 and interferons (IFNs) could induce functional thyroid damage in patients affected by melanoma or renal cell carcinoma (RCC), by causing thyroiditis.[12–16] Increased levels of thyroid autoantibodies[14,15] or hypothyroidism without autoantibodies[16,17] have been associated with improved outcome in patients with

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Key points

- The reported incidence of sunitinib-induced hypothyroidism is 53–85% and 36–46% in retrospective or prospective studies, respectively, and 18% in patients treated with sorafenib
- Mechanisms of hypothyroidism induced by TKIs include drug-induced atrophy of the thyroid through inhibition of its vascularization, drug-induced thyroiditis, reduced synthesis of thyroid hormones, progressive depletion of the thyroid's functional reserve and inhibition of the thyroidal iodine uptake
- Whether TKI-related hypothyroidism is mediated by inhibition of the VEGF pathway or of other molecular pathways is unknown
- In patients treated with sunitinib or sorafenib, routine thyroid function testing at baseline, and measurement of serum thyroid stimulating hormone level on day 1 at the start of every new treatment cycle is recommended
- Levothyroxine is the standard treatment for overt hypothyroidism and is recommended in some patients with subclinical hypothyroidism; overt or subclinical hypothyroidism *per se* does not justify the withdrawal of TKI therapy
- Thyroid function test should be included in routine toxicity assessment of TKIs under clinical evaluation; however, the clinical relevance of early diagnosis of hypothyroidism in patients with TKIs is still controversial

metastatic RCC or melanoma treated with interleukin-2 or IFNα (Table 2). The antiangiogenic agents thalidomide[18,19] and lenalidomide[20] can cause hypothyroidism, possibly through an immune-mediated subacute destructive thyroiditis.[18,20] Bexarotene is used to treat cutaneous T-cell lymphoma and has been found to induce secondary hypothyroidism.[21] Locoregional head and neck radiotherapy is associated with immediate and long-term adverse effects, which can include hypothyroidism, thyroid neoplasm, and Graves disease.[22–24]

TKIs and hypothyroidism

Imatinib

Available data suggest that some TKIs worsen pre-existing hypothyroidism or cause *de novo* hypothyroidism. Imatinib inhibits the kinase activity of the tyrosine kinases ABL, c-KIT and platelet-derived growth factor receptor. The influence of daily 400–800 mg imatinib on levothyroxine therapy (LT4-Rx) was reported in a cohort of 11 patients (10 with medullary thyroid carcinoma and 1 with gastrointestinal stromal tumor [GIST]).[25] Among the patients with medullary thyroid carcinoma, eight underwent thyroidectomy and received LT4-Rx and three had thyroid carcinoma *in situ*. Thyroid function was evaluated before, during and 2 weeks after therapy with imatinib or LT4-Rx. Symptoms of hypothyroidism occurred in all patients who had undergone thyroidectomy, but not in those with an intact thyroid. Patients who had undergone thyroidectomy had markedly elevated TSH levels, and required an increase of LT4-Rx during imatinib dosing. The decline in TSH values after treatment suggests that imatinib might be the causative agent. Imatinib-associated complications led to the discontinuation of therapy in 36% of patients.

Sunitinib

Sunitinib is an oral, multitarget inhibitor of VEGF receptor 1 (VEGFR-1), VEGFR-2, FMS-like tyrosine kinase 3 (FLT3), colony stimulating factor 1 receptor (CSF1R), RET, KIT, and platelet-derived growth factor receptor. This agent has been found to influence the thyroid function of patients with GIST or RCC. In total, 2 of 56 patients with RCC and a history of well-controlled hypothyroidism, and 7 of 21 patients with imatinib-resistant GIST, had a worsening hypothyroidism during sunitinib treatment.[26,27] De Groot *et al.*[28] reported the case of a woman with GIST who was resistant to imatinib and received LT4-Rx after thyroidectomy and ^{131}I-ablation for follicular thyroid carcinoma. The patient's dose of LT4-Rx needed to be increased after sunitinib treatment. The marked increase in TSH levels indicates a potential interference of sunitinib with thyroid hormone action at the pituitary level.[28]

Desai and coauthors[29] prospectively evaluated the thyroid function tests (TFTs) in a phase I/II study of sunitinib therapy in 42 patients with imatinib-resistant GIST. Most patients received 50 mg sunitinib daily every 4–6 weeks, each consisting of 2–4 weeks of sunitinib followed by 2 weeks of washout. Initially, TFTs were performed only if clinically indicated. Thereafter, serum TSH was evaluated before each sunitinib cycle. In total, 42 patients with normal baseline TFTs who received at least three sunitinib treatment cycles for a median of 37 weeks were evaluated. Abnormal serum TSH concentrations were documented in 26 patients (62%). Sunitinib caused persistent primary hypothyroidism in 15 patients (36%), after an average of 50 weeks of therapy (range 12–94 weeks). Seven additional patients (17%) experienced transient, mild TSH elevation (5.0–7.0 mU/l). In four patients TSH was suppressed, but they discontinued treatment before the TFT could be repeated. Of 15 patients with hypothyroidism, 6 (40%) had at least one TSH value below 0.5 mU/l before developing the condition, which suggests a thyroiditis-induced thyrotoxicosis. The risk of hypothyroidism increased with the duration of sunitinib therapy. Subclinical or overt hypothyroidism was observed in 4 of 22 patients (18%) who received sunitinib for 9 months, and in 5 of 17 patients (29%) who received sunitinib for longer than 12 months.[29] In patients treated for longer than 96 weeks, 90% developed increased levels of TSH. The mean time to development of hypothyroidism was 50 weeks. Among the patients with TSH concentrations greater than 10 mU/l, none had spontaneous biochemical resolution. During the titration of LT4-Rx, serum TSH values remained elevated for a median of 17 weeks (range 4–117 weeks). The TSH concentrations returned to normal in all patients who received conventional doses of LT4-Rx. Interestingly, in two patients with hypothyroidism and normal baseline TFTs, ultrasonography revealed atrophic thyroid tissue, which suggests destructive thyroiditis. This clinical trial was the first to report the prevalence of sunitinib-related hypothyroidism.[29] Notably, the study was retrospective, and the study design precluded identification of the prevalent mechanisms of sunitinib-associated thyroid dysfunction.

Rini and colleagues[26] described thyroid abnormalities in a retrospective study of 66 patients with metastatic

Table 1 | Tyrosine kinase inhibitors approved for clinical use or under advanced clinical evaluation

Drug	Main TKs targeted	Tumors	Prevalent adverse effects	Clinical development
Imatinib	ABL1/2, PDGFRα/β, KIT	CML, GIST	Edema, nausea, myelosuppression, immunosuppression	Approved
Dasatinib	ABL1/2, PDGFRα/β, KIT, Src family	CML	Myelosuppression, edema, pleural/pericardial effusion, panniculitis, bleeding, QT prolongation	Approved
Nilotinib	ABL1/2, PDGFRα/β, KIT	CML, ALL, GIST	Myelosuppression, hyperbilirubinemia, rash, QT prolongation	Phase I–III
Sunitinib	VEGFR1–3, KIT, PDGFRα/β, RET, CSF1R, FLT3	RCC, GIST, various	Hemorrhage, hypertension, adrenal dysfunction, hypothyroidism	Approved for RCC and GIST Phase II–III trials in other tumor types
Sorafenib	RAF/MEK/ERK, VEGFR-2, KIT, VEGFR-3, FLT3, FGFR-1, RET, c-MET, PDGFRβ	RCC, HCC, various	Skin rash, hypertension, hemorrhage, acute coronary syndrome, hypothyroidism	Approved for RCC and HCC Phase II–III trials in other tumor types
Gefitinib	EGFR	NSCLC	Skin rash, diarrhea, nausea, interstitial lung disease	Approved
Erlotinib	EGFR	NSCLC, pancreas	Skin rash, diarrhea, nausea, interstitial lung disease	Approved
Lapatinib	EGFR, ERBB2	Breast	Skin rash, diarrhea	Approved
Axitinib	VEGFR1–3, PDGFR, KIT	Breast, RCC, melanoma, CRC, NSCLC, pancreas, thyroid	Hypertension, fatigue, nausea, diarrhea, vomiting, headache, hemoptysis, stomatitis, erythema	Phase II–III
Vatalanib	VEGFR1–3, PDGFR, KIT	CRC, breast, brain, pancreas	Hypertension, fatigue, nausea, vomiting, dizziness, ataxia	Phase II–III
Vandetanib (ZD6474)	VEGFR2, EGFR, RET	NSCLC, brain, CRC, thyroid	Rash, diarrhea, proteinuria, hypertension, asymptomatic QTc prolongation	Phase II–III
AEE788	VEGFR1–2, EGFR, HER2	Various	Diarrhea, fatigue, anorexia, rash, nausea, vomiting	Phase I–II
Motesanib	VEGFR1–3, PDGFR, KIT	Thyroid	Diarrhea, hypertension, fatigue, nausea, diarrhea, vomiting, hypothyroidism	Phase II–III

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CRC, colorectal cancer; CSF1R, colony stimulating factor 1 receptor; FGFR-1, fibroblast growth factor receptor 1, FLT3, FMS-like tyrosine kinase 3; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; RCC, renal-cell carcinoma; VEGFR, vascular endothelial growth factor receptor.

RCC treated with sunitinib. In total, 30 patients were pretreated with cytokine-based therapy (6 of whom were treated with bevacizumab), and 30 patients were treatment naive. All patients received the standard sunitinib dose of 50 mg daily for 4 weeks, followed by 2 weeks off therapy. TFT assessment, including free-thyroxine index, was initiated in 29 patients (and subsequently in another 37 patients) as a routine laboratory assessment at baseline and on day 28 of every even-numbered cycle. Of the 66 patients, 56 (85%) had one or more TFT abnormality. These abnormalities were consistent with hypothyroidism in all patients and primarily included the elevation of TSH, decreased levels of T3 and, less commonly, decreases in T4 and/or of the free-thyroxine index. TFT abnormalities were detected early (the median time of detection was at cycle 2).[26] Among patients with abnormal TFTs, signs and symptoms related to hypothyroidism were found in 47 patients (84%). These symptoms included fatigue, cold intolerance, anorexia, periorbital edema, fluid retention, and alterations in skin or hair. LT4-Rx was given at the discretion of the physician, on the basis of the degree of biochemical abnormality and/or clinical symptoms. A resolution of biochemical abnormalities occurred in all 17 patients treated with LT4-Rx, and an improvement of symptoms was recorded in 9 patients. Thyroglobulin antibodies were measured in 44 patients and were abnormal in 13 (30%). No association was observed between the presence of thyroglobulin antibodies and either the incidence or severity of TFT abnormalities.

The development of thyroid autoantibodies was associated with improved outcomes in patients with metastatic RCC who received interleukin-2 or IFNα immunotherapy.[14,15] Limitations of this study include the small number of patients assessed, the absence of control participants, and the fact that baseline TFT measurements were lacking in some patients. Since a proportion of patients were pretreated with cytokines, it would be of interest to know whether hypothyroidism is prevalent in pretreated or naive patients.

Table 2 | Agents that interfere with thyroid function and metabolism of thyroid hormones

Drugs	Mechanisms
Monovalent anions (thiocyanate, perchlorate)	Inhibit iodide transport into the thyroid
Thionamide drugs (propylthiouracil, methimazole)	Inhibit thyroid peroxidase; prevent thyroid hormone synthesis. Propilthyouracil inhibits the conversion of T4 to T3 in peripheral tissues
Calcium	Binds T4 and reduces its absorption
Nitrate, bromine, rubidium, and fluorine	Alteration of the synthesis of thyroid hormone
Lithium carbonate	Inhibits iodide binding and hormonal release (has a synergistic action with iodide)
Aminoglutethamide, phenylbutazone 2,3-dimercaptopropanolol	Inhibit the synthesis and secretion of thyroid hormones and/or iodide transport into the thyroid
Iodinate contrast agents (ipodate, iopanoic acid)	Inhibit conversion from T4 to T3 by inhibiting both type I and type II 5'-deiodinase, which causes a profound decrease in the serum T3 concentration and an increase in the reverse T3 and T4 levels, with a slight increase or no change in T4 values; decrease hepatic uptake of T4; inhibition of T3 binding to its nuclear receptor
Salicylates	Compete for thyroid hormones binding sites on serum TTR and TBG
Rifampin	Increases thyroid hormone clearance through the induction of hepatic microsomal enzymes
Phenobarbital, carbamazepin, diphenylhydantoin	Increase thyroid hormone clearance through the induction of hepatic microsomal enzymes; compete with thyroid hormones binding to TBG; accelerate the conjugation and liver clearance of T4/T3; probably enhanced conversion of T4 to T3
Glucocorticoids	Variable effects on the endocrine status of the individual, depending on the dose, type of glucocorticoid, and the route of administration. Decrease TBG and increase TTR; inhibit the deiodination of T4 and probably reverse T3; suppress TSH secretion; increase in renal clearance of iodide
Estrogens	All hyperestrogenisms are accompanied by an increase in TBG and decrease in TTR concentration. Effects on TSH controversial. Free hormone levels unaffected
Androgens and anabolic steroids	Decrease concentration of TBG and level of T4 and T3. Free hormone levels unaffected
Heparin, halophenate, fenclofenac	Compete with binding of thyroid hormone to its carrier proteins in serum
Amiodarone	Marked decrease in serum T3 level; increasing reverse T3 and modest T4 level elevation. Basal and TRH-stimulated TSH levels are increased by inhibition of both type I and type II 5'-deiodinase, which results in a marked reduction of T3 generation from T4
L-Dopa and bromocryptine, some α-adrenergic blockers, and opiates	Increase synthesis of T3 from T4 in the brain, while alcohol and opiates block the breakdown of T3 in the brain
Dopamine antagonists, cimetidine, clomifene, spirolactone	Interfere with the normal dopaminergic suppression of the hypothalamic–pituitary axis; increased TSH secretion not associated with significant metabolic alterations
Interferons, interleukins	Autoimmune thyroid disease
Cytotoxic agents (L-asparaginase, 5-fluorouracil, mitotane, alkylating agent and epipodophyllotoxine combinations)	Affect thyroid hormone transport proteins and TBG synthesis
Cisplatin, vincristine, carmustine, lomustine, procarbazine in combinations with other cytotoxic agents or radiotherapy	Unknown
Thalidomide, lenolidomide	Immune-mediated subacute destructive thyroiditis
Somatostatin	Abnormal serum TSH levels are rare; response of TSH to the administration of TRH might be altered. In patients with elevated TSH levels, TSH might be significantly reduced
Tamoxifen	In postmenopausal women increases TBG, T4 and T3 levels. Effects on TSH controversial
Raloxifen	Increases TBG and slightly increases T4

Abbreviations: TBG, thyroxin binding globulin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; TTR, transthyretin.

Feldman and coauthors[30] reported hypothyroidism in 14 (18%) of the 80 patients enrolled in a prospective clinical trial that investigated the efficacy of sunitinib in metastatic RCC. TSH levels were obtained only from symptomatic patients and ranged from 6.0 to 146.4 mU/l (normal range 0.35–5.5 mU/l). Hypothyroidism was detected after a median time of 10 months of therapy (range 1–26 months), with fatigue being the predominant

Table 3 | Incidence of hypothyroidism and alterations of thyroid function tests[a]

Reference	Tumor type	Study design	TKI used	Number of patients	Previous treatment	Number of patients with hypothyroidism (%)	Number of patients with altered TFTs (%)
Desai *et al.* (2006)[29]	GIST	Prospective	Sunitinib	42	Imatinib	15 (36)	26 (62)[c]
Rini *et al.* (2007)[26]	RCC	Retrospective/ Prospective	Sunitinib	66 (R:29; P:37)	Naive (30) Cytokines (30) Bevacizumab (6)	47 of 56 (84)[b]	56 (85)
Schoeffski *et al.* (2006)[31]	GIST, RCC	Retrospective/ Prospective	Sunitinib	33 (R:14; P:19)	Not reported	8 of 14 (57); R 7 of 19 (37); P	21 (64)
Wong *et al.* (2007)[27]	GIST, others	Retrospective	Sunitinib	40	Not reported	21 (53)	ND
Mannavola *et al.* (2007)[32]	GIST	Prospective	Sunitinib	24	None	17 (71)[d]	ND
Tamaskar *et al.* (2008)[33]	RCC	Retrospective	Sorafenib	39	Not reported	7 (18)	16 (43)

[a]Important follow-up data, in particular for transient elevation of TSH, are not available in the majority of studies. [b]Data referred to patients with signs and symptoms possibly related to hypothyroidism (fatigue, cold intolerance, anorexia, periorbital edema, fluid retention, and changes in skin or hair). [c]Only TSH was evaluated. [d]46% stable, 25% transient TSH elevation. Abbreviations: GIST, gastrointestinal stromal tumors; ND, not determined; RCC, renal-cell carcinoma; R/P, initially retrospective followed by prospective evaluation; TKI, tyrosine kinase inhibitor; TFTs, thyroid function tests; TSH, thyroid-stimulating hormone.

symptom. The authors underlined that the lower incidence of hypothyroidism reported might depend on the fact that TFT assessment was performed only in symptomatic patients.[30]

Schoeffski and colleagues[31] evaluated the prevalence of hypothyroidism in patients with GISTs or metastatic RCC treated with sunitinib at the standard dose. TFTs included assessment of serum TSH, T3, free-thyroxine index and thyroid antibodies (thyroglobulin antibodies, thyroid peroxidase anitbodies, and TSH-receptor antibodies). Of 33 evaluable patients, data from 14 (who all had GISTs) were analyzed retrospectively, and data from the other 19 patients were analyzed prospectively (8 of whom had GISTs and 11 had RCC). Of the 19 patients, 7 (37%) showed elevated TSH levels (>5 mU/l) during treatment. From a cohort of patients, data were analyzed retrospectively and showed that eight patients (57%) developed hypothyroidism after a median treatment duration of 44 weeks. In total, 3 of the 11 patients with RCC had increased TSH levels after 6 weeks of treatment.[31]

Wong *et al.*[27] explored the potential effects of sunitinib on thyroid function in a cohort of 40 patients affected by different tumor histotypes, the majority of whom had GISTs that were pretreated with imatinib. The authors found that new-onset or worsening hypothyroidism occurred in 21 of 40 patients (53%) patients who underwent TFTs. Patients developed elevated TSH levels after a median of 5 months of treatment (range 1–36 months). The median TSH level was 21.4 mU/L (range 4.6–174 mU/L). Wong *et al.* assessed the influence of sunitinib on peroxidase activity *in vitro* by testing its effects on guaiacol oxidation and protein iodination caused by lactoperoxidase. The potency of sunitinib antiperoxidase activity was about 25% of that noted with propylthiouracil. The authors proposed that the antithyroid effect of sunitinib is mediated by the inhibition of peroxidase activity, which is involved in the synthesis of thyroid hormone. Major limitations of the study are its retrospective design and the absence of sequential measurement of TFT at defined intervals. In fact, only 8 of 40 patients had baseline TFTs measured. This selection bias could have resulted in an inaccurately high incidence of hypothyroidism.

In a prospective phase I–II study, Mannavola *et al.*[32] evaluated TFT (serum TSH, free T3 and T4, thyroglobulin, thyroglobulin antibodies and thyroid peroxidase antibodies) in 24 patients with GISTs who were treated with sunitinib (4 weeks of 50 mg daily and 2 weeks of withdrawal). Urinary iodine was measured in 18 patients and urinary fluorine was assessed in 10 patients. Thyroid ultrasonography and echo-color Doppler were performed, both at enrollment and after a variable number of treatment cycles. To study thyroid function, ^{123}I thyroidal uptake and scintigraphy were performed in six unselected patients at the end of the treatment and withdrawal periods. Hypothyroidism was documented in 46% of patients, and a transient elevation of TSH levels in 25% of cases. The overall prevalence of elevated TSH levels after sunitinib was 71%. At onset, hypothyroidism was subclinical in all but one patient with Hashimoto thyroiditis, the only one with detectable antithyroid autoantibodies. TSH levels were found to fluctuate according to whether treatment was given or withdrawn, and progressively increased during treatment. In most cases, hypothyroidism showed a progressive worsening, but in a few cases a sudden development of severe hypothyroidism was observed. The normal echographic and echo-color-Doppler patterns, obtained both at baseline and during treatment, indicate that hypothyroidism is unlikely to be the consequence of a direct toxic effect on thyroid cells or secondary to an autoimmune process. Inhibition of iodine uptake seems to be a more likely explanation for hypothyroidism. Indeed, radioiodine uptake impairment has been demonstrated by a reduced

Table 4 | Proposed mechanisms to explain TKI-related hypothyroidism or increase in levothyroxine requirement

Mechanisms	Clinical evidence	Preclinical data
Sunitinib		
Destructive thyroiditis[23]	Absence of thyroid tissue on ultrasonography in two patients who developed hypothyroidism during sunitinib treatment	No specific data
Prevention of VEGF binding to normal thyroid cells and/or impairing thyroid blood flow resulting in thyroiditis and thyroid dysfunction[26]	No specific data	No specific data
Reduced synthesis of thyroid hormones[27]	Inhibition of thyroid peroxidase activity	No specific data
Inhibition of iodine uptake[32]	^{123}I thyroidal uptake and scintigraphy	No specific data
RET impairment[33]	No specific data	Cellular abnormalities in thyroid-targeted transgenic mice[61]
Progressive damage to thyroid function	The majority of hypothyroid patients with TKI-related hypothyroidism, pretreated with cytokines[26] or imatinib[29]; in first-line trial of sunitinib vs interferon-α,[49] sorafenib vs placebo[50] and combination of sorafenib with interferon-α,[51] thyroid dysfunction not included in the most frequent adverse effects	No specific data
"Off target" effects	No specific data	No specific data
Sorafenib		
Prevention of VEGF binding to normal thyroid cells and/or impairing thyroid blood flow resulting in thyroiditis and thyroid dysfunction[26]	No specific data	No specific data
RET impairment[33]	No specific data	RET encodes a membrane TK receptor in thyroid C cells[33]
"Off target" effects	No specific data	No specific data
Axitinib		
Inhibition of VEGFR-2 and VEGFR-3 leading to thyroid capillary regression[57,58]	No specific data	Dose dependent thyroid capillary regression; TSH was 19-fold higher than in the control group. Most of the capillaries re-grew within 2 weeks after treatment withdrawn (reversible process)[58]
Imatinib		
Increase of the nondeiodination clearance (induction of hepatic microsomal enzymes)[25]	Increased requirement of levothyroxine	No specific data

Abbreviations: RET, rearranged during transfection; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor; TSH, thyroid stimulating hormone; VEGFR, vascular endothelial growth factor receptor.

uptake at the end of treatment periods, with a partial or total recovery during the withdrawal phase. Of particular interest was the observation of a blunted early ^{123}I uptake curve, which suggests an alteration in the uptake phase rather than in the organification process. The authors noted that after sunitinib withdrawal, TSH levels returned to the normal range in a maximum of 60 days.

Sorafenib

Sorafenib is an oral multikinase inhibitor that inhibits the kinase activity of RAF/MEK/ERK, VEGFR-2 and VEGFR-3, FLT3, fibroblast growth factor receptor 1, RET, c-MET, platelet-derived growth factor receptor β, KIT and other receptors involved in tumor progression and angiogenesis. Tamaskar *et al.*[33] retrospectively investigated the incidence of TFT abnormalities in 39 patients with metastatic RCC treated with 400 mg sorafenib twice daily. Most patients had received at least one prior treatment. Of the 39 patients, 16 (41%) had one or more TFT values outside the laboratory normal reference range during treatment with sorafenib. The median timing of the abnormal test was 1.8 months (range 0.6–7.3 months). Biochemical hypothyroidism occurred in 7 of 39 patients (18%) during treatment, which was first observed 2–4 months after sorafenib initiation. Six of these patients had mild TSH level elevations (5.5–10.0 mU/l). Another patient showed a rapid onset of hypothyroidism with TSH level rising from 5.74 to 160.64 mU/l, and T3 level

decreasing from 72 to 49 ng/dl over 1.5 months. One patient had normal TSH concentration (2.42 mU/l) but low T3 and T4 at 4 months after starting sorafenib treatment, and these abnormalities worsened over the next 4 months with further reductions of T3 and T4 levels, and abnormal TSH (9.930 mU/l). Both these patients received LT4-Rx. In two of the seven hypothyroid patients thyroglobulin antibody titres increased; two had persistent TSH elevation and one showed normalization of TSH.

Box 1 | Definition and clinical aspects of overt and subclinical hypothyroidism

Hypothyroidism is defined as a low level of serum T4 and an elevated level of serum thyroid stimulating hormone (TSH). In some cases individuals with hypothyroid symptoms, high TSH (>10 mU/l), and low normal fT4 are diagnosed as having overt hypothyroidism.[2,3] Overt hypothyroidism affects 1.4–2.0% of women and 0.1–0.2% of men.[4] The prevalence is higher among elderly women, with autoimmune thyroiditis being most common.[5,6] Other causes include congenital thyroid disorders, previous thyroid surgery and irradiation, pituitary and hypothalamic diseases, and dietary iodine deficiency. Drugs such as lithium carbonate and amiodarone have been shown to induce hypothyroidism (Table 1). Hypothyroidism is associated with nonspecific constitutional and neuropsychiatric complaints or with hypercholesterolemia, hyponatremia, hyperprolactinemia, or hyperhomocysteinemia. Severe, untreated hypothyroidism can lead to heart failure, psychosis, and coma. Levothyroxine replacement is the treatment for overt hypothyroidism and is highly effective and safe.[4]

Subclinical hypothyroidism is defined as a serum TSH above the defined upper limit of the reference range when serum free T4 concentration is normal.[2] The prevalence of subclinical hypothyroidism is 7.5–8.5% in women and 2.8–4.4% in men, and can be as high as 15–20% in women over the age of 60 years and 8% in elderly men.[7] Potential risk factors include type I diabetes mellitus, a family history of thyroid disease, previous head and neck cancer, or Hodgkin disease treated with external-beam radiation.[55] Typical symptoms are consistent with declining metabolic functions, and range from fatigue to evident clinical symptoms, including changes in mental function and memory, lethargy, weight gain, cold intolerance, constipation, and goitrous enlargement. Atypical presentations such as weight loss, hearing impairment, tinnitus, and carpal tunnel syndrome can occur, especially in the elderly. In individuals not taking thyroid hormone, serum TSH returns to normal levels after 1 year of follow-up in approximately 5% of cases only.[5] The management of subclinical thyroid dysfunction is controversial. Little evidence exists that early replacement treatment improves clinical course. Elderly patients with high antithyroid antibody titers are at high risk of rapid development of overt hypothyroidism, so early intervention with levothyroxine treatment is indicated.[8]

Mechanisms for TKI-related hypothyroidism

Nondeiodination clearance has been suggested as the most likely mechanism responsible for imatinib-induced hypothyroidism in patients who receive LT4-Rx replacement therapy.[25] Several drugs (such as phenobarbital, phenytoin, carbamazepine, rifampicin, and nicardipine) can increase thyroid hormone clearance through the induction of hepatic microsomal enzymes, including mixed function oxygenases and uridine diphosphate–glucuronosyltransferases,[34] and can cause hypothyroidism in patients who undergo LT4-Rx.[35–38] Imatinib is a potent competitive inhibitor of several mixed function oxygenases (CYP2C9, CYP2D6, and CYP3A4/5),[39] and the induction of uridine diphosphate–glucuronosyltransferases has been hypothesized to be a possible mechanism of interference of imatinib on levothyroxine metabolism.[25]

Regarding the pathogenesis of sunitinib-induced hypothyroidism, several possible mechanisms have been suggested (Table 3). The most plausible are destructive thyroiditis,[29] the reduced synthesis of thyroid hormones related to inhibition of thyroid peroxidase activity,[27] the drug-induced regression of the gland vascular bed with significant capillary alteration and reduction in density.[26] The role of VEGF in thyroid signaling is uncertain.[40,41] Unlike treatment with antiangiogenic TKIs, bevacizumab is not associated with altered thyroid homeostasis.[42,43] Other factors, such as platelet-derived growth factor-α and c-KIT, have roles in thyroid homeostasis, but so far no data have been published. In addition, *in vitro* experiments showed that VEGF reduces TSH-induced iodine uptake by thyroid cells, and inhibition of VEGF restores iodine uptake.[42] A direct effect of sunitinib on the sodium and iodide symporter or TSH receptor has been hypothesized by Mannavola *et al.*[32] The inhibition of iodine uptake by the thyroid, caused by changes in the sodium and iodide symporter, seems to be the more likely mechanism. In fact, the authors demonstrated that the TSH receptor is not likely to be involved because other endocrine axes operating through the cAMP pathway were not affected. Fluorine, which is present in sunitinib, could act on the sodium and iodide symporter as a competitive inhibitor for iodine uptake, similarly to other monovalent anions. Nonetheless, normal fluorine levels were observed in treated patients.[32]

The postulated mechanism that causes hypothyroidism in patients treated with sorafenib might be related to VEGFR inhibition, by preventing binding of VEGF to normal thyroid cells, and/or impairing thyroid blood flow, which results in thyroiditis.[29,44] The lower incidence of thyroid dysfunction observed in patients treated with sorafenib compared with that in those receiving sunitinib could be related to the degree of inhibition of these receptors by these two drugs.[45] Additionally, the inhibition of kinase activity of certain oncogenes involved in thyroid cells physiology, such as *RET*[46,47] and *BRAF*,[48] might contribute to the hypothyroidism observed.

Available data indicate that the development of hypothyroidism might be related to a progressive damage to thyroid function, or the consequence of a reduction of the thyroid functional reserve (Table 4). The majority of available data on hypothyroidism secondary to TKIs are from patients previously treated with cytokines[26] or imatinib.[29] In addition, two studies that explored the activity of sunitinib versus IFNα[49] or sorafenib versus placebo,[50] and another study that evaluated the combination of sorafenib with IFNα[51] as first-line treatment of patients with metastatic RCC, did not report thyroid dysfunction among the most frequent adverse effects.

Treatment of TKI-related hypothyroidism

Primary hypothyroidism might be the basis of sunitinib-induced fatigue. Unfortunately, the exact role of hypothyroidism and thyroid dysfunction in fatigue remains

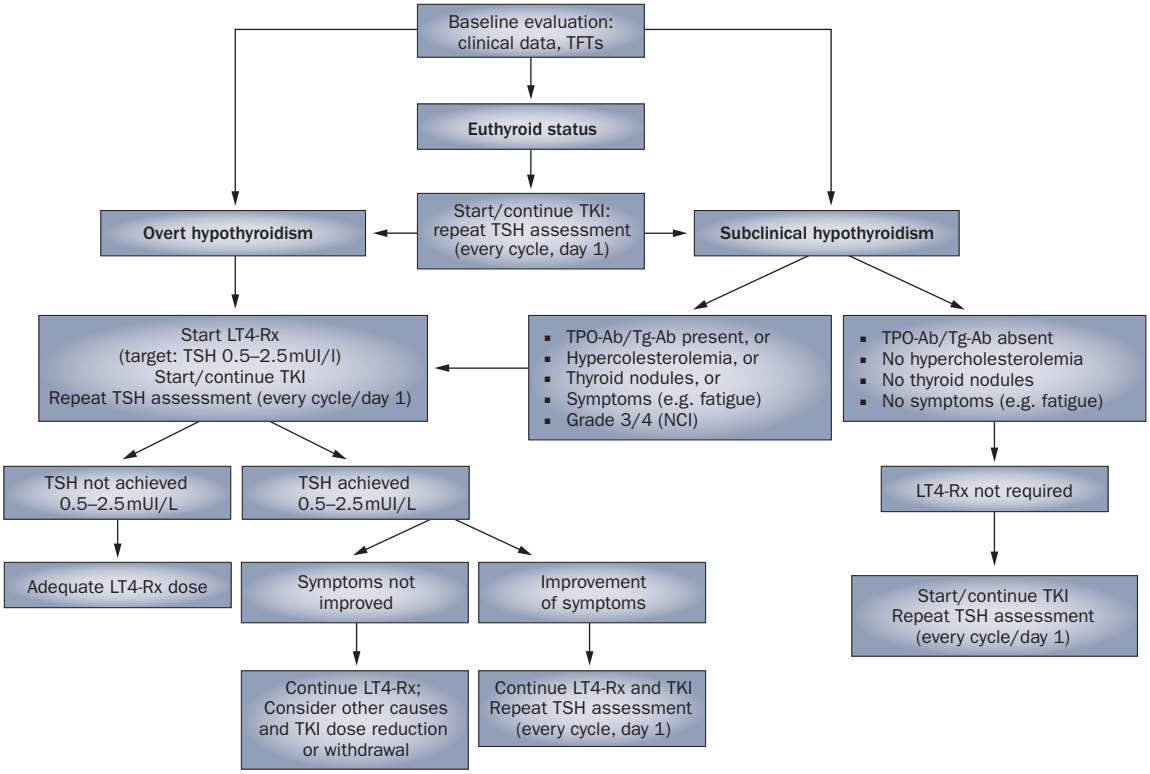

Figure 1 | Flow chart to show the proposed decision-making sequence for the management of hypothyroidism in patients receiving tyrosine kinase inhibitors. Abbreviations: LT4-Rx, levothyroxine therapy; TFTs, thyroid function tests; Tg-Ab, thyroglobulin antibodies; TKI, tyrosine kinase inhibitors; TPO-Ab, thyroid peroxidase anitbodies; TSH, thyroid stimulating hormone.

undetermined. The high incidence of fatigue might be explained by an off-target effect of TKIs on thyroid function, in terms of overt or subclinical hypothyroidism. It has been suggested that several of the symptoms related to TKIs and shared with hypothyroidism can be safely treated with levothyroxine (Box 1). However, only a proportion of patients who developed hypothyroidism while receiving sunitinib and LT4-Rx (50–79%) had resolution of symptoms related to hypothyroidism.[33]

The therapeutic relevance of early diagnosis of hypothyroidism or even subclinical hypothyroidism is as yet unknown. Definitive data on the advantage of early treatment of subclinical hypothyroidism are not available from prospective studies. Thyroid function should be systematically assessed at baseline and during the course of treatment, both within and outside of clinical trials.[52] Serum TSH and free T4 levels should be measured with thyroid antibodies at baseline, and serum TSH levels should also be measured on day 1 of each cycle. Patients with elevated TSH can be managed safely and effectively with thyroid hormone replacement; thus, hypothyroidism by itself would not induce a discontinuation or reduction of the anticancer treatment (Figure 1).[29,52]

Garfield *et al.*[53] warned that some preclinical, epidemiological and clinical evidence suggests that LT4-Rx is permissive for tumor growth. Possible actions of thyroid hormones on cancer cells include the amplification of *EGFR*, phosphorylation of insulin-like growth factor 1 receptor, stimulation of migration, a direct trophic effect on tumor cells, cell-specific antiapoptotic activity and angiogenesis.[54] The American Thyroid Association suggests that thyroid hormone therapy should be withheld in asymptomatic hypothyroid patients (i.e. in those with serum TSH concentrations of 5–10 mU/l) on the basis of data from a scientific review.[55] Of note, some patients with serum TSH levels above 10 mU/l have few or no symptoms of hypothyroidism and, therefore, do not necessarily need LT4-Rx.[56] Whether the American Thyroid Association recommendations are valid in patients with cancer is, however, unclear. To this aim therapeutic trials of low-dose thyroid hormone replacement have been proposed.[56]

We propose a decision-making sequence for the management of hypothyroidism in patients undergoing therapy with TKIs (Figure 1). Patients who have overt hypothyroidism and subclinical hypothyroidism with increased thyroid peroxidase or thyroglobulin antibody titres, hypercholesterolemia, thyroid nodules or hypothyroid complaints (e.g. fatigue) should be treated with LT4-Rx to achieve the 'target value' of TSH (0.5–2.5 mU/l). The withdrawal of the TKI should be considered only if other possible causes of symptoms shared with hypothyroidism are excluded and the euthyroid status has been reached and maintained. As a consequence, the presence

of overt or subclinical hypothyroidism does not permit the withdrawal of TKI therapy.

Conclusions and future areas of research

Hypothyroidism induced by sunitinib and sorafenib, and the interference with LT4-Rx of imatinib, and probably sunitinib, are unexpected toxicities that should be considered carefully in clinical practice. Axitinib induced hypothyroidism in preclinical studies,[57,58] but this result has not yet been reported in clinical trials. The incidence of primary hypothyroidism as an adverse effect of TKIs is variable. In retrospective studies the incidence of sunitinib-induced hypothyroidism ranges from 53 to 85%,[26,27,31] whereas in prospective studies the incidence ranges from 36 to 71%.[29,32] Sorafenib has been reported to cause hypothyroidism in 18% of patients with metastatic RCC in only one study.[33]

Several possible mechanisms that lead to sustained TKI-related thyroid toxic effects have been suggested, but pharmacological and preclinical data are lacking. Understanding whether sunitinib-related or sorafenib-related hypothyroidism is dependent on the drug's direct mechanism of action (i.e. inhibition of VEGFR-2, KIT, BRAF, RET etc.), or because of indirect effects on other targets (mechanism-independent toxic effects) will be important to optimize therapy. Accurate studies on the mechanism-dependent and mechanism-independent toxic effects of new cancer drugs in clinical settings will not only lead to safer treatment with targeted agents, but could also provide the opportunity to achieve a better therapeutic index in individual patients.[59] Unfortunately, the majority of published studies on hypothyroidism as an adverse effect of TKIs are observational. A common problem shared by all the studies is the small number of patients evaluated, which reduces the statistical power of each single study and the reliability of the conclusions.

Prospective trials are needed to explore the incidence of overt and subclinical hypothyroidism and thyroid dysfunction during therapy with sunitinib, sorafenib and other TKIs. To this aim, epidemiological and biological features of thyroid function should be carefully tested. TSH levels progressively rise with age. The prevalence of subclinical hypothyroidism might, therefore, be significantly overestimated unless an age-specific range for TSH is used.[60] In future studies biological correlative features (such as the role of key genes for thyroid function) would help to define the molecular mechanisms of TKI-induced damage of thyroid function.

It would be of interest to compare the incidence of thyroid toxic effects induced by TKIs when used as first-line treatment to that following sequential therapy. If thyroid dysfunction is more frequent in patients after second-line or third-line treatments, a 'summation effect' related to the sequential treatments might be responsible. In addition, because TKI-related hypothyroidism seems to be a long-term adverse effect, the investigational use of TKIs in the adjuvant setting should take into account this issue, and monitoring thyroid function in patients treated with sunitinib or sorafenib should be mandatory.

The clinical relevance of overt hypothyroidism, the value of thyroid hormone replacement in individuals with abnormal TSH after TKI therapy, and the correct timing of replacement therapy need to be defined more accurately and should be evaluated prospectively with appropriately designed clinical trials. To this aim, a closer collaboration between oncologists and endocrinologists will improve the majority of the above issues and improve the therapies used and quality of life for patients with cancer.

Review criteria

The PubMed and MEDLINE databases were searched for articles published before 30 April 2008. Electronic early-release publications are also included. Only articles published in English were considered. The search terms were: "hypothyroidism" or "thyroid dysfunction" in association with "tyrosine kinase inhibitors", "sunitinib", "sorafenib", "imatinib", "erlotinib", "lapatinib", "axitinib", "motesanib", "anti-angiogenic agents" or "targeted therapy". Proceedings from the 2000–2007 conferences of the American Society of Clinical Oncology, European Society of Medical Oncology and the Endocrine Society were searched for relevant abstracts.

1. Lacouture, M. E. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat. Rev. Cancer* **6**, 806–812 (2006).
2. Ross, D. S. Serum thyroid-stimulating hormone measurement for assessment of thyroid function and disease. *Endocrinol. Metab. Clin. North. Am.* **30**, 245–264 (2001).
3. Vanderpump, M. P. *et al.* The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin. Endocrinol. (Oxf.)* **43**, 55–68 (1995).
4. Roberts, C. G. & Ladenson, P. W. Hypothyroidism. *Lancet* **363**, 793–803 (2004).
5. Parle, J. V., Franklyn, J. A., Cross, K. W., Jones S. C. & Sheppard, M. C. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin. Endocrinol. (Oxf.)* **34**, 77–83 (1991).
6. Robuschi, G., Safran, M., Braverman, L. E., Gnudi, A. & Roti, E. Hypothyroidism in the elderly. *Endocr. Rev.* **8**, 142–153 (1987).
7. Hollowell, J. G. *et al.* Serum TSH T_4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J. Clin. Endocrinol. Metab.* **87**, 489–499 (2002).
8. Heymann, R. & Brent, G. A. Rapid progression from subclinical to symptomatic overt hypothyroidism. *Endocr. Pract.* **11**, 115–119 (2005).
9. Yeung, S. C., Chiu, A. C., Vassilopoulou-Sellin, R. & Gagel, R. F. The endocrine effects of nonhormonal antineoplastic therapy. *Endocr. Rev.* **19**, 144–172 (1998).
10. Stuart, N. S., Woodroffe, C. M., Grundy, R. & Cullen, M. H. Long-term toxicity of chemotherapy for testicular cancer—the cost of cure. *Br. J. Cancer* **61**, 479–484 (1990).
11. Sutcliffe, S. B., Chapman, R. & Wrigley, P. F. Cyclical combination chemotherapy and thyroid function in patients with advanced Hodgkin's disease. *Med. Pediatr. Oncol.* **9**, 439–448 (1981).
12. Mandac, J. C., Chaudhry, S., Sherman, K. E. & Tomer, Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. *Hepatology* **43**, 661–672 (2006).
13. Vassilopoulou-Sellin, R. Endocrine effects of cytokines. *Oncology (Williston Park)* **8**, 43–46 (1994).
14. Atkins, M. B. *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N. Engl. J. Med.* **318**, 1557–1563 (1988).
15. Franzke, A. *et al.* Autoimmunity resulting from cytokine treatment predicts long-term survival in patients with metastatic renal cell cancer. *J. Clin. Oncol.* **17**, 529–533 (1999).
16. Weijl, N. I. *et al.* Hypothyroidism during immunotherapy with interleukin-2 is associated with antithyroid antibodies and response to treatment. *J. Clin. Oncol.* **11**, 1376–1383 (1993).

17. Krouse, R. S. *et al.* Thyroid dysfunction in 281 patients with metastatic melanoma or renal carcinoma treated with interleukin-2 alone. *J. Immunother. Emphasis Tumor Immunol.* **18**, 272–278 (1995).
18. Badros, A. Z. *et al.* Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. *Am. J. Med.* **112**, 412–413 (2002).
19. de Savary, N., Lee, R. & Vaidya, B. Severe hypothyroidism after thalidomide treatment. *J. R. Soc. Med.* **97**, 443 (2004).
20. Stein, E. M. & Rivera, C. Transient thyroiditis after treatment with lenalidomide in a patient with metastatic renal cell carcinoma. *Thyroid* **17**, 681–683 (2007).
21. Sherman, S. I. *et al.* Central hypothyroidism associated with retinoid X receptor-selective ligands. *N. Engl. J. Med.* **340**, 1075–1079 (1999).
22. Hancock, S. L., McDougall, I. R. & Constine, L. S. Thyroid abnormalities after therapeutic external radiation. *Int. J. Radiat. Oncol. Biol. Phys.* **31**, 1165–1170 (1995).
23. Loeffler, J. S., Tarbell, N. J., Garber, J. R. & Mauch, P. The development of Graves' disease following radiation therapy in Hodgkin's disease. *Int. J. Radiat. Oncol. Biol. Phys.* **14**, 175–178 (1988).
24. Petersen, M., Keeling, C. A. & McDougall, I. R. Hyperthyroidism with low radioiodine uptake after head and neck irradiation for Hodgkin's disease. *J. Nucl. Med.* **30**, 255–257 (1989).
25. de Groot, J. W., Zonnenberg, B. A., Plukker, J. T., van Der Graaf, W. T. & Links, T. P. Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin. Pharmacol. Ther.* **78**, 433–438 (2005).
26. Rini, B. I. *et al.* Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J. Natl Cancer Inst.* **99**, 81–83 (2007).
27. Wong, E. *et al.* Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. *Thyroid* **17**, 351–355 (2007).
28. de Groot, J. W., Links, T. P. & van der Graaf, W. T. Tyrosine kinase inhibitors causing hypothyroidism in a patient on levothyroxine. *Ann. Oncol.* **17**, 1719–1720 (2006).
29. Desai, J. *et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann. Intern. Med.* **145**, 660–664 (2006).
30. Feldman, D. R., Martorella, A. J., Robbins, R. J. & Motzer, R. J. Re: hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J. Natl Cancer Inst.* **99**, 974–975 (2007).
31. Schoeffski, P. *et al.* Sunitinib-related thyroid dysfunction: a single-center retrospective and prospective evaluation. *J. Clin. Oncol.* **24** (**Suppl 18**), 3092 (2006).
32. Mannavola, D. *et al.* A novel tyrosine kinase inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. *J. Clin. Endocrinol. Metab.* **92**, 3531–3534 (2007).
33. Tamaskar, I. *et al.* Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. *Ann. Oncol.* **19**, 265–268 (2008).
34. Curran, P. G. & DeGroot, L. J. The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. *Endocr. Rev.* **12**, 135–150 (1991).
35. Surks, M. I. & Sievert, R. Drugs and thyroid function. *N. Engl. J. Med.* **333**, 1688–1694 (1995).
36. Schröder-van der Elst, J. P. *et al.* Effects of 5, 5'-diphenylhydantoin on the metabolic pathway of thyroid hormone in rats. *Eur. J. Endocrinol.* **136**, 324–329 (1997).
37. De Luca, F. *et al.* Changes in thyroid function tests induced by 2 month carbamazepine treatment in L-thyroxine-substituted hypothyroid children. *Eur. J. Pediatr.* **145**, 77–79 (1986).
38. Takasu, N., Takara, M. & Komiya, I. Rifampin-induced hypothyroidism in patients with Hashimoto's thyroiditis. *N. Engl. J. Med.* **352**, 518–519 (2005).
39. Novartis Pharmaceuticals Corporation. Gleevec (imatinib mesylate): full prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ (2002).
40. Wang, J. F. *et al.* Presence and possible role of vascular endothelial growth factor in thyroid cell growth and function. *J. Endocrinol.* **157**, 5–12 (1998).
41. Gordon, M. S. *et al.* Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J. Clin. Oncol.* **19**, 843–850 (2001).
42. Willett, C. G. *et al.* Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: continued experience of a phase I trial in rectal cancer patients. *J. Clin. Oncol.* **23**, 8136–8139 (2005).
43. Willett, C. G. *et al.* Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat. Med.* **10**, 145–147 (2004).
44. Grossmann, M., Premaratne, E., Desai, J. & Davis, I. D. Thyrotoxicosis during sunitinib treatment for renal cell carcinoma. *Clin. Endocrinol. (Oxf.)* **69**, 669–672 (2008).
45. Mendel, D. B. *et al. In vivo* antitumour activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin. Cancer Res.* **9**, 327–337 (2003).
46. Takahashi, M. *et al.* Cloning and expression of the ret proto-oncogene encoding a receptor tyrosine kinase with two potential transmembrane domains. *Oncogene* **3**, 571–578 (1988).
47. Nakamura, T., Ishizaka, Y., Nagao, M., Hara, M. & Ishikawa, T. Expression of the ret proto-oncogene product in human normal and neoplastic tissues of neural crest origin. *J. Pathol.* **172**, 255–260 (1994).
48. Chiloeches, A. & Marais, R. Is BRAF the Achilles' heel of thyroid cancer? *Clin. Cancer Res.* **12**, 1661–1664 (2006).
49. Motzer, R. J. *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N. Engl. J. Med.* **356**, 115–124 (2007).
50. Escudier, B. *et al.* Sorafenib in advanced clear-cell renal-cell carcinoma. *N. Engl. J. Med.* **356**, 125–134 (2007).
51. Ryan, C. W. *et al.* Sorafenib with interferon alfa-2b as first-line treatment of advanced renal carcinoma: a phase II study of the Southwest Oncology Group. *J. Clin. Oncol.* **22**, 3296–3301 (2007).
52. Wolter, P., Dumez, H. & Schöffski, P. Laboratory abnormalities suggesting thyroid dysfunction in patients treated with sunitinib. *Ann. Intern. Med.* [http://www.annals.org/cgi/eletters/145/9/660] (2007).
53. Garfield, D. H., Hercbergs, A. & Davis, P. J. Re: Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J. Natl Cancer Inst.* **99**, 975–976 (2007).
54. Davis, P. J. *et al.* Cell surface receptor for thyroid hormone and tumor cell proliferation. *Exp. Rev. Endocrinol. Metabol.* **1**, 753–761 (2007).
55. Surks, M. I. *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA.* **291**, 228–238 (2004).
56. Garfield, D., Hercbergs, A. & Davis P. Unanswered questions regarding the management of sunitinib-induced hypothyroidism. *Nat. Clin. Pract. Oncol.* **4**, 674–675 (2007).
57. Baffert, F. *et al.* Cellular changes in normal blood capillaries undergoing regression after inhibition of VEGF signaling. *Am. J. Physiol. Heart Circ. Physiol.* **290**, H547–H559 (2006).
58. Kamba, T. *et al.* VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. *Am. J. Physiol. Heart Circ. Physiol.* **290**, H560–H576 (2006).
59. Maitland, M. L. & Ratain, M. J. Terminal ballistics of kinase inhibitors: there are no magic bullets. *Ann. Intern. Med.* **145**, 702–703 (2006).
60. Surks, M. I. & Hollowell, J. G. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J. Clin. Endocrinol. Metab.* **92**, 4575–4582 (2007).
61. Cho, J. Y., Sagartz, J. E., Capen, C. C., Mazzaferri, E. L. & Jhiang, S. M. Early cellular abnormalities induced by RET/PTC1 oncogene in thyroid-targeted transgenic mice. *Oncogene* **18**, 3659–3665 (1999).