

Endocrine side effects of broad-acting kinase inhibitors

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Abstract

Targeted therapy in oncology consists of drugs that specifically interfere with abnormal signaling pathways that are dysregulated in cancer cells. Tyrosine kinase inhibitors (TKIs) take advantage of unique oncogenes that are activated in certain types of cancer, and also target common mechanisms of growth, invasion, metastasis, and angiogenesis. However, many kinase inhibitors for cancer therapy are somewhat nonselective, and most have additional mechanisms of action at the cellular level, which are not completely understood. The use of these agents has increased our knowledge of important side effects, of which the practicing clinician must be aware. Recently, proposed endocrine-related side effects of these agents include alterations in thyroid function, bone metabolism, linear growth, gonadal function, fetal development, and glucose metabolism, and adrenal function. This review summarizes the most recent data on the endocrine side effects of TKIs.

Endocrine-Related Cancer (2010) 17 R233–R244

Introduction

Dysregulated kinase signaling is invariably involved in the pathogenesis of all types of malignancies. Therefore, enormous efforts are being devoted to the development of small molecule drugs that regulate the abnormal cancer ‘kinome’. Protein tyrosine kinases (TKs) catalyze the phosphorylation of specific tyrosine residues on their substrate proteins. TKs are key regulators of signaling pathways involving cellular proliferation, differentiation, and apoptosis (Schlessinger 2000, Krause & Van Etten 2005). Small molecule TK inhibitors (TKIs) are rationally designed compounds that affect TK-dependent oncogenic pathways. They are promising treatments for the therapy of malignant disease, and offer excellent targets for selective inhibition (Krause & Van Etten 2005). These agents potentially provide a relatively high therapeutic window with low toxicity in comparison with conventional cytotoxic chemotherapy. However, as we gain experience with the use of TKIs, we are becoming aware of important side effects. This review will outline the endocrine-related side effects associated with TKIs in order to bring the

practicing clinician up to date with the current status of the field.

TKIs have become more widespread in use as targeted therapy for a variety of malignancies (Zhang *et al.* 2009). One of the first TKIs to demonstrate effectiveness, imatinib, has activity against the BCR–ABL oncoprotein, and has been successful in the treatment of chronic myeloid leukemia (CML; Ren 2005, Jabbour *et al.* 2007). Imatinib is also approved for the treatment of recurrent or metastatic gastrointestinal stromal tumors (GISTs), in which the c-KIT or platelet-derived growth factor receptor α (PDGFR α) TKs may be constitutively activated (Rubin *et al.* 2007). More recently, TKIs have been used in the treatment of neuroendocrine tumors (Kulke *et al.* 2008, Raymond 2010). Oncogenic kinases that have been implicated in the development of thyroid cancer, such as rearranged during transfection (RET) proto-oncogene and B-RAF (a proto-oncogene serine/threonine protein kinase), have emerged as targets for TKI therapy (Lodish & Stratakis 2008, Sherman 2009a). For patients with medullary or differentiated thyroid cancer unresponsive to conventional treatment,

TKIs are currently being used in a number of clinical trials (Gupta-Abramson *et al.* 2008, Sherman *et al.* 2008, Fox *et al.* 2009, Kloos *et al.* 2009, Schlumberger *et al.* 2009, Wells *et al.* 2010). Further use of these agents for other types of malignancies is outlined in Table 1.

There are more than 500 different protein kinases encoded by the human genome; almost all of these kinases phosphorylate substrate proteins via their catalytic ATP-binding region (Daub 2010). The TKs include the epidermal growth factor receptor (EGFR), the vascular endothelial growth factor receptors 1 and 2 (VEGFR1 and VEGFR2), and the downstream signaling mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK) pathway, among others (Sebolt-Leopold 2008, Tortora *et al.* 2008). PDGFRA, fibroblast growth factor receptor, and serine–threonine kinase mammalian target of rapamycin are additional kinases implicated in oncogenesis (Alvarez *et al.* 2006, Meric-Bernstam & Gonzalez-Angulo 2009). In papillary thyroid cancer (PTC), somatic rearrangement of the *RET* proto-oncogene leads to activated forms of RET, and germline mutations of the *RET* receptor are pathogenic in medullary thyroid cancer (MTC; Ciampi & Nikiforov

2007, Wells & Santoro 2009). Activation of the B-Raf proto-oncogene serine/threonine protein kinase occurs frequently in adult PTC (Xing 2005).

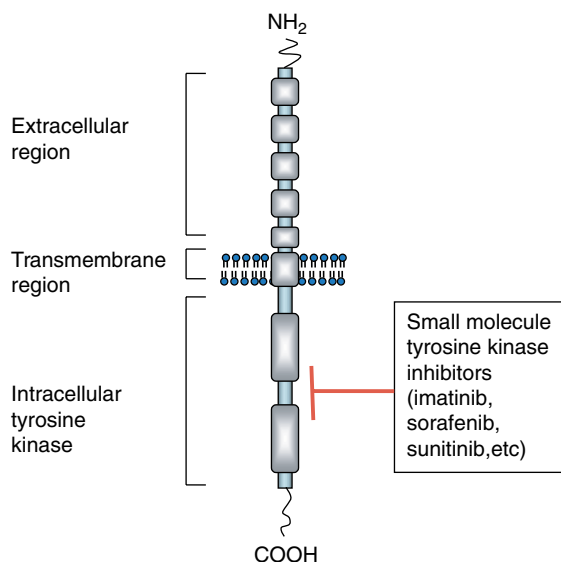
Among the different classes of protein kinases, there is a conservation of the structure of the ATP-binding site. TKIs act as small molecules with structural similarity to ATP, which serve to disrupt the catalytic activation of TKs (Fig. 1). As a result of this homology, many TKIs may have inhibitory activity against a broad range of protein kinases. Many kinase inhibitors are less selective than initially thought and often affect multiple signaling pathways (Fabian *et al.* 2005, Karaman *et al.* 2008, Daub 2010).

TKIs are administered orally and cause a number of side effects including fatigue, hypertension, rash, impaired wound healing, myelosuppression, and diarrhea (Widakowich *et al.* 2007). The overall toxicity of TKIs, while less life-threatening than conventional cytotoxic chemotherapy, nevertheless is common, and may require dose reduction. Recently, proposed endocrine-related side effects of these agents include alterations in thyroid function, bone metabolism, linear growth, gonadal function, fetal development, and glucose metabolism, and adrenal function (Fig. 2).

Table 1 Major tyrosine kinase inhibitors in clinical use

Drug	Tumors treated	Main tyrosine kinases targeted	Stage of clinical development
Imatinib	CML, chronic eosinophilic leukemia, Philadelphia-positive ALL, and GIST	bcr–abl, c-KIT and PDGFRA	FDA approved
Dasatinib	CML and Philadelphia chromosome-positive ALL	SRC family TK, bcr–abl, c-KIT and PDGFRA	FDA approved
Nilotinib	CML	bcr–abl, c-KIT and PDGFRA	FDA approved
Sunitinib	GIST and RCC	VEGFR2, PDGFRB, c-KIT and FLT3	FDA approved
Sorafenib	RCC and hepatocellular carcinoma	RAF/MEK/ERK VEGFR2/PDGFRs	FDA approved
Gefitinib	NSCLC	EGFRs	FDA approved
Erlotinib	NSCLC pancreatic cancer	EGFRs	FDA approved
Lapatinib	HER2-positive breast cancer	EGFR, ErbB2, Erk-1 and -2 and AKT kinases	FDA approved
Axitinib	Pancreatic, breast RCC, NSCLC, melanoma, thyroid and renal	VEGFRs and PDGFRs	Phases II–III
Vandetanib	NSCLC, myeloma, thyroid cancer and glioma	VEGFRs, EGFRs and RET	Phases II–III
Vatalanib	Colorectal cancer, pancreatic, neuroendocrine and glioblastoma multiforme	VEGFRs, PDGFRs, c-KIT and c-Fms	Phases II–III
AEE788	Glioblastoma multiforme	EGFR, HER2 and VEGF2	Phase I/II
Motesanib	GIST, breast cancer, neuroendocrine tumors, thyroid, colorectal and NSCLC	VEGFRs, PDGFRs, c-KIT and RET	Phase II/III
Dovitinib	Melanoma, RCC, breast and prostate	FGFR3, VEGFR, PDGFR3, FLT-3 and c-KIT	Phase I/II
Tivozanab	RCC, breast, colorectal and NSCLC		Phase II/III

All information may be accessed at <http://www.cancer.gov>; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; GIST, gastrointestinal stromal tumor; RCC, renal cell carcinoma; NSCLC, nonsmall cell lung carcinoma; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; FLT-3, Fms-related tyrosine kinase 3.



TKIs prevent receptor phosphorylation by competing with ATP binding in the activation domain, inhibiting downstream signal transduction

Figure 1 Schematic of structure and function of tyrosine kinase receptor and its small molecule inhibitors.

Thyroid function

The increased use of TKIs has raised the awareness of adverse effects on thyroid hormone function and/or thyroid hormone metabolism, as outlined in Table 2. As a result of these studies, it is now recommended that all patients starting therapy with TKIs have their thyroid function tested prospectively (Sherman 2009b, Torino *et al.* 2009). Other types of anticancer therapies have also been associated with thyroid dysfunction, including radiation to the pituitary and thyroid, and treatment with synthetic retinoid X receptor agonist autoantibodies (Sherman *et al.* 1999, Garcia-Serra *et al.* 2005, Darzy & Shalet 2009). Hypothyroidism has also been reported after therapy with the angiogenesis inhibitor thalidomide (Badros *et al.* 2002). Therapy with interleukin-2 (IL-2) and interferon- α has been reported to induce thyroid dysfunction and thyroid autoantibodies (Weijl *et al.* 1993).

The effect of TKIs in thyroid function was first noted in 2005 with the use of imatinib, which inhibits the TK activity of the ABL, c-KIT, and PDGFRA kinases. In eight MTC patients treated with imatinib, all of whom had previously undergone thyroidectomy, marked elevations in TSH up to a mean of $384 \pm 228\%$ of the upper limit were noted (de Groot *et al.* 2005). Free thyroxine (T_4) was decreased but generally remained within the reference range. Despite doubling the

average dosage of levothyroxine, thyroid functions were normalized in only three out of eight patients. The authors described associated symptoms that could be considered consistent with hypothyroidism, including fatigue and edema. However, they also pointed out that it was difficult to distinguish whether these were caused by hypothyroidism, other underlying disease, or imatinib itself. Interestingly, in this initial description of thyroid dysfunction associated with TKIs, the patients had no thyroid glands (since they had undergone thyroidectomies for their tumors); therefore, ‘thyroid dysfunction’ could be better described as ‘alterations in TSH and free T_4 ’ or ‘worsening postsurgical hypothyroidism’, because the thyroid gland itself could not be implicated in the pathophysiology. One study evaluating the thyroid function of 68 patients with CML and intact thyroid glands who received imatinib did not find any adverse effect on thyroid function, suggesting that perhaps the effect of imatinib was unique to patients surgically rendered athyroid (Dora *et al.* 2008). Motesanib, a TKI with inhibitory effects on VEGFR, PDGFRA, c-KIT, and RET, was also associated with marked exacerbation of postsurgical hypothyroidism in a phase II thyroid cancer trial. In this study, 60–70% of patients exhibited elevated TSH values, with 22% of patients defined as having clinical hypothyroidism, and a mean levothyroxine dosage increase in 30% was required to maintain normal TSH levels (Pacini *et al.* 2007).

A number of other studies have followed thyroid functions in patients receiving TKIs who have intact thyroid glands (Table 2). Sorafenib inhibits the kinase activity of RAF, mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK), extracellular signal-regulated kinase (ERK), VEGFR2 and PDGFR. Tamaskar *et al.* studied the incidence of thyroid function alterations in patients with metastatic renal cell cancer (RCC): hypothyroidism developed in 7 of 39 patients (18%), and was first observed 2–4 months after initiation of sorafenib.

The TKI most frequently associated with hypothyroidism is sunitinib, which targets VEGFRs, PDGFRs, KIT, and RET. Desai *et al.* (2006) prospectively obtained thyroid function tests (TFTs) in 42 patients with GIST who were receiving sunitinib. Abnormal elevations in TSH were seen in 26 patients (62%), while persistent hypothyroidism was documented in 15 patients (36%). The average length of time to first peak elevation of TSH was 50 weeks of therapy (range 12–94 weeks). The investigators were able to normalize TSH in all patients with levothyroxine therapy. The authors suggested destructive thyroiditis as a possible mechanism of sunitinib-induced hypothyroidism, as

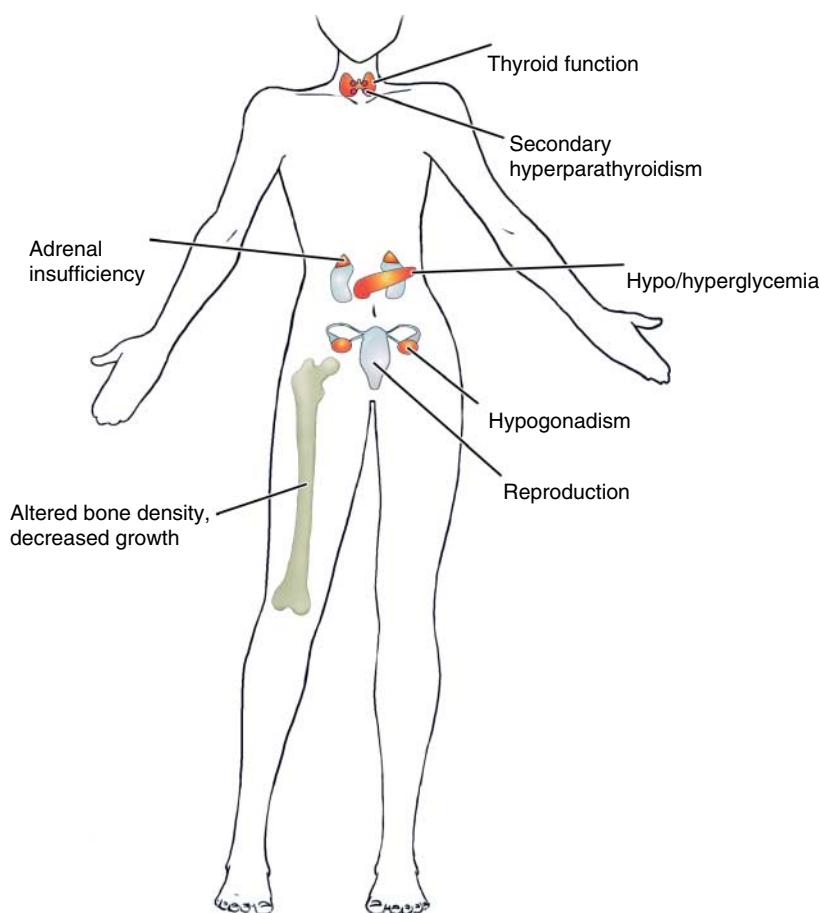


Figure 2 Endocrine organs involved in side effects of tyrosine kinase inhibitors.

6 out of 15 patients with hypothyroidism had a TSH level below $0.5 \mu\text{IU/ml}$ prior to developing hypothyroidism. In addition, two patients were found to have atrophic thyroid tissue on ultrasound, thought to be consistent with thyroiditis. Rini *et al.* (2007) evaluated thyroid abnormalities in 66 patients with RCC treated with sunitinib. The results of this study are complicated by the fact that 30 of the patients received treatment with cytokine-based therapy (Weijl *et al.* 1993). In total, 56 of the 66 patients (85%) developed hypothyroidism; symptoms that can be associated with hypothyroidism, such as cold intolerance, fatigue, edema, dry skin, and thinning hair, were seen in 47 out of 66 patients (84%). This study also proposed thyroiditis as a possible mechanism for the observed abnormalities as thyroglobulin antibodies were found in 13 out of the 44 patients in whom they were measured. Two other reports have also demonstrated sunitinib-induced hypothyroidism associated with destructive thyroiditis (Faris *et al.* 2007, Grossmann *et al.* 2008). However, a number of other studies have shown recovery of TSH values to the normal range following treatment with

sunitinib, which does not support the hypothesis of destructive thyroiditis (Grossmann *et al.* 2008, Wolter *et al.* 2008).

Schoeffeski *et al.* (2006) measured thyroid functions in 19 patients with RCC and GIST receiving sunitinib. Of these patients, 7 out of 19 (37%) showed elevated TSH during treatment, while 8 out of the 14 (57%) patients went on to develop hypothyroidism after a median duration of 44 weeks. Wong *et al.* (2007) evaluated the prevalence of hypothyroidism in a cohort of 40 patients with GIST, 53% of whom exhibited hypothyroidism after a median of 5 months of treatment with sunitinib. This study was limited by the lack of baseline thyroid function data in the majority of patients, making it difficult to determine the true underlying incidence of thyroid dysfunction.

Martorella *et al.* (2006) reported a 20% incidence of hypothyroidism in a group of 39 patients with RCC treated with sunitinib; however, a complicating factor is that all patients had prior treatment with IL-2. Shaheen *et al.* (2006) evaluated TFTs in 55 patients with RCC, 73% of whom developed hypothyroidism.

Table 2 Studies reporting hypothyroidism in patients receiving tyrosine kinase inhibitor (TKI) therapy

References	Tumor type	TKI used	Subjects with TFTs (n)	Hypothyroidism (%)
Desai <i>et al.</i> (2006)	GIST	Sunitinib	42	36
Rini <i>et al.</i> (2007)	RCC	Sunitinib	66	85
Schoeffski <i>et al.</i> (2006)	RCC and GIST	Sunitinib	33	37 prospectively 57 retrospectively
Wong <i>et al.</i> (2007)	GIST	Sunitinib	40	53
Martorella <i>et al.</i> (2006)	RCC	Sunitinib	39	20
Sabatier <i>et al.</i> (2009)	RCC	Sunitinib	54	68
Shaheen <i>et al.</i> (2006)	RCC	Sunitinib	55	73
Mannavola <i>et al.</i> (2007)	GIST	Sunitinib	24	46
Chu <i>et al.</i> (2007)	GIST	Sunitinib	36	14
Wolter <i>et al.</i> (2008)	RCC and GIST	Sunitinib	59	27
Tamaskar <i>et al.</i> (2008)	RCC	Sorafenib	39	18
de Groot <i>et al.</i> (2005)	GIST and MTC	Imatinib	11	73
de Groot <i>et al.</i> (2007)	MTC	Imatinib	15	60
Sherman <i>et al.</i> (2008)	DTC	Motesanib	93	22
Dora <i>et al.</i> (2008)	CML	Imatinib	68	0

ALL, acute lymphoblastic leukemia; GIST, gastrointestinal stromal tumor; RCC, renal cell carcinoma; MTC, medullary thyroid cancer; DTC, differentiated thyroid cancer; CML, chronic myeloid leukemia.

Sabatier *et al.* performed a prospective observational analysis of hypothyroidism during sunitinib therapy in metastatic RCC and found that 68% of the 54 patients developed hypothyroidism. In a study by Mannavola *et al.* (2007), 46% of patients with GIST on sunitinib treatment developed hypothyroidism requiring therapy with levothyroxine, while 25% exhibited transient TSH elevation. Thyroid ultrasound scans and iodine-123 (^{123}I) thyroidal uptake were performed at the end of several periods of sunitinib treatment. They found that ^{123}I uptake was significantly reduced at the end of treatment periods, with partial or total normalization when therapy with TKIs was discontinued. The authors suggested that the underlying mechanism of sunitinib-induced thyroid dysfunction was impaired iodine uptake.

Two cases of RCC patients diagnosed with a nodular thyroid gland were observed to have marked shrinkage of the thyroid gland during treatment with sunitinib (Rogiers *et al.* 2010). Thyroid gland volume reduction was measured via computed tomography (CT) scan, showing progression to near complete disappearance of the gland in one of the two patients. The authors hypothesize that TKI-induced thyroid dysfunction may be due to capillary regression induced by VEGF inhibition. A recent case report described a patient with RCC who developed hypothyroidism while on sunitinib and was found to develop an atrophic thyroid with marked reduction in vascularity (Makita *et al.* 2010). However, disputing these findings is a study by Mannavola *et al.* (2007) who performed thyroid ultrasounds on 11 patients both before and during sunitinib treatment, and did not detect changes in thyroid gland volume.

The mechanism by which TKIs cause thyroid dysfunction remains unclear. A number of *in vitro* and animal studies have been performed to try and characterize the mechanism of TKI-induced hypothyroidism. Wong *et al.* (2007) performed *in vitro* assays to measure the effect of sunitinib on peroxidase activity, and found that sunitinib had antiperoxidase activity 25–30% as potent as propylthiouracil. They propose that sunitinib acts directly on the thyroid gland via inhibition of peroxidase activity and thyroid hormone synthesis. Salem *et al.* (2008) evaluated the pathological mechanism of sunitinib-induced hypothyroidism in rat thyroid cell cultures, and found that incubation with sunitinib for 24 h caused a dose-related increase in ^{125}I -iodide uptake, suggesting that inhibition of iodine uptake is unlikely to be the mechanism of sunitinib-induced hypothyroidism.

The definition of hypothyroidism was somewhat variable in the studies reviewed, and some studies lacked complete TFT data in all patients. Postulated mechanisms are presented in Table 3. Interestingly, alterations in thyroid function tests have also been observed in clinical trials of thyroid cancer patients who have undergone thyroidectomy. This would certainly argue against a direct role of the thyroid gland in the mechanism of the effect of TKIs on TSH levels. Thus, some of the proposed mechanisms to explain the elevated TSH cannot explain the observed alterations of TFTs in studies of postthyroidectomy patients. One mechanism to explain worsening TSH elevation in postthyroidectomy patients would be an indirect effect of sunitinib on the metabolism of thyroid hormone, or with thyroid hormone action at the

Table 3 Proposed mechanisms of tyrosine kinase inhibitor-induced hypothyroidism

Decrease in enteric thyroid hormone absorption
Increased hepatic metabolism of T ₄ and T ₃
Inhibition of T ₄ deiodination
Impaired iodide uptake
Stimulation of T ₄ and T ₃ clearance
Destructive thyroiditis
Direct inhibition of thyroid peroxidase activity
Capillary regression induced by VEGF inhibition
Interference with thyroid hormone action at the pituitary gland level

pituitary level. It is plausible that the different types of TKIs have more than one mechanism affecting thyroid functions, but it remains more likely that there is a universal drug class effect of these medications that have yet to be clarified.

Unanswered questions remain regarding the optimal management of TKI-induced hypothyroidism. Baseline thyroid function tests should be performed before the initiation of TKI therapy, and TFTs should be frequently monitored during treatment with TKIs. Levothyroxine treatment should be started when clinical hypothyroidism develops. However, the management of asymptomatic subclinical hypothyroidism (TSH 5–10 µIU/ml) is uncertain in cancer patients in whom symptoms of hypothyroidism, such as fatigue, might overlap with symptoms of the malignancy and its treatment. Individuals with elevated TSH can be effectively managed with thyroid hormone replacement, such that hypothyroidism alone is not an indication for dose reduction or discontinuation of TKI therapy (Torino *et al.* 2009). Additional prospective clinical trials are necessary to investigate this important endocrine side effect and to determine the underlying molecular mechanism of TKI-related hypothyroidism.

Altered bone density and secondary hyperparathyroidism

A number of recent studies have demonstrated altered bone and mineral metabolism in patients receiving imatinib; however, to date, this affect has not been reported in other TKIs (Berman *et al.* 2006, Grey *et al.* 2006, Osorio *et al.* 2007, Fitter *et al.* 2008). As patients taking TKIs often continue the treatment indefinitely, clinicians need to be aware of the potential long-term effects of these agents on the skeleton. A 2-year prospective clinical study of the biochemical and skeletal effects of imatinib revealed secondary hyperparathyroidism and decreased bone turnover during prolonged treatment with imatinib (O’Sullivan *et al.* 2009). In nine

patients with *bcr-abl*-positive CML, therapy with imatinib was associated with a biphasic change in bone turnover, with an initial stimulation of bone formation followed by a period of suppression of bone resorption and formation. Bone mineral density in the cohort studied was stable or increased during the first 2 years of therapy, along with the development of mild secondary hyperparathyroidism (O’Sullivan *et al.* 2009). Two additional studies have demonstrated increased cortical bone mineralization in CML patients treated with imatinib (Fitter *et al.* 2008, Jonsson *et al.* 2008).

The effects of TKIs on bone mineral metabolism and bone remodeling are hypothesized to be due to unspecific inhibition of tyrosine kinases expressed by osteoclasts and osteoblasts, such as c-KIT and PDGFRA (Berman *et al.* 2006). *In vitro* studies have shown that the TKI dasatinib can cause dysregulation of bone remodeling via inhibition of osteoclasts (Vandyke *et al.* 2010). Additional *in vitro* studies revealed that imatinib promotes osteoblast differentiation by inhibiting PDGFR signaling and osteoclastogenesis (O’Sullivan *et al.* 2007).

Linear growth

Because of the small numbers of pediatric patients receiving single drug therapy with TKIs, it has not been feasible to conduct large-scale clinical trials to gain information about the effects of long-term therapy with TKIs on linear growth in childhood and adolescence. Angiogenesis is controlled in part by soluble factors such as VEGF and PDGF. Imatinib was shown to inhibit PDGF-induced cell proliferation and activity in chondrocyte cultures *in vitro* (Vandyke *et al.* 2009). In mouse models, VEGF has been linked to key steps in cartilage remodeling, ossification, and angiogenesis during endochondral bone formation (Gerber *et al.* 1999). Recent *in vivo* studies in rats showed narrowing of the growth plate at the proximal tibia in imatinib-treated animals (Vandyke *et al.* 2009). In a mouse model, imatinib treatment had an antiresorptive effects on osteoclasts that impaired the length of tubular bone, particularly in prepubertal animals (Suttorp *et al.* 2008). These studies have raised concern for the potential effects of TKIs on longitudinal growth in children.

Three recently published case studies report decelerated growth in prepubertal CML patients undergoing imatinib therapy (Mariani *et al.* 2008, Kimoto *et al.* 2009, Schmid *et al.* 2009). In one such case, the authors reported an 11-year-old boy who experienced a dramatic reduction in growth rate from 4.3 to 1.5 cm per year after initiating imatinib therapy

(Mariani *et al.* 2008). In another case, a 6-year-old girl had significantly decreased growth velocity after being started on imatinib therapy for CML; the same patient returned to an increased growth rate after cessation of imatinib: during 4 years of imatinib therapy, the patient's height SDS decreased from -0.7 to -2.7 (Kimoto *et al.* 2009). Finally, a third case reported a 5-year-old-girl whose height fell from the 74th percentile to the 9th percentile after 3 years of treatment with imatinib (Schmid *et al.* 2009). Additional larger scale clinical studies are necessary to draw meaningful conclusions about the effect of imatinib and other TKIs on linear growth in children.

Hypogonadism and ovarian insufficiency

A number of case reports have presented a possible association between gynecomastia and TKI use. One described a 69-year-old patient with metastatic RCC who developed painful gynecomastia while on sunitinib therapy; this gynecomastia was partially reduced while off therapy and resumed when sunitinib was reinitiated (Ballardini *et al.* 2009). Another report describes a patient with CML initiated on imatinib at the age of 11 years. Beginning at age 14, this patient had progressive increase in FSH and a decrease in inhibin-B, along with the development of gynecomastia (Mariani *et al.* 2008). Another report described the development of gynecomastia in a 42-year-old male on imatinib for GIST (Kim *et al.* 2005). In one case of gynecomastia in a 70-year-old male after treatment with dasatinib for CML, tamoxifen was added as combination therapy with subsequent reduction in gynecomastia (Caocci *et al.* 2008). Another study looked at testosterone levels in 38 men receiving imatinib for CML at baseline and during treatment. Seven cases of gynecomastia were noted (18% of patients), with associated significant decrease in testosterone concentrations (Gambacorti-Passerini *et al.* 2003). The mechanism by which sunitinib and other TKIs may induce gynecomastia is unknown, although c-KIT and PRGFRA are expressed in the testis, and are involved in the production of testosterone (Basciani *et al.* 2002). Imatinib has been shown to inhibit Leydig cell tumor growth in rat models, and this may be due to the inhibition of proliferation and ligand-stimulated phosphorylation of PDGFRA and c-KIT (Basciani *et al.* 2005).

One case of primary ovarian insufficiency during imatinib therapy was recently reported (Christopoulos *et al.* 2008); however, the report was later challenged as being overly speculative (Malozowski *et al.* 2008). In animal models, fertility in female rats has not been adversely affected by imatinib, and experience with the

drug has shown pregnancies in women taking TKIs (Hensley & Ford 2003, Robinson *et al.* 2007). Future long-term evaluation of the effects of TKIs on ovarian function and fertility are required.

Pregnancy and TKIs

As the use of TKIs becomes more widespread, the safety of these agents during pregnancy has been called into question in light of the potential risks to the fetus. Few data exist on the effect of TKIs on fetal growth and development, and current recommendations call for the use of effective contraception in young women undergoing treatment. However, in cases where alternative therapy or stopping therapy are not acceptable alternatives, these agents have been used during pregnancy, and some reports are available on outcomes of pregnancies in women taking TKIs. A review on the use of targeted treatment with TKIs during pregnancy was recently published (Robinson *et al.* 2007). Imatinib has been linked with low birth weight, and both erlotinib and lapatinib have been associated with oligohydramnios, necessitating the close ultrasound follow-up of growth and amniotic fluid index in these patients.

Adrenal insufficiency

Although overt adrenal insufficiency has not been reported in patients receiving TKIs, adrenal damage was observed in animal studies (Pfizer). Adrenal toxicity was reported in repeat dose studies performed in rats and monkeys at plasma exposures as low as 0.7 times the area under the curve observed in clinical studies. A number of histological changes of the adrenal gland were noted, including hemorrhage, necrosis, congestion, hypertrophy, and inflammation. In clinical studies, CT/magnetic resonance imaging obtained in 336 patients after exposure to one or more cycles of sunitinib failed to demonstrate evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in ~ 400 patients across multiple clinical trials of sunitinib, with only one patient found to have consistently abnormal test results during treatment. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12–16.4 $\mu\text{g}/\text{dl}$ (normal $> 18 \mu\text{g}/\text{dl}$) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency (Pfizer).

The hypothalamic–pituitary–adrenal (HPA) axis was evaluated in 25 patients with CML treated with imatinib using glucagon stimulation testing as well as low dose (1 μg) ACTH testing. Twelve (48%) of

patients were defined as HPA deficient in this study (defined as a peak serum cortisol level $<18 \mu\text{g/dl}$ measured 30 min after i.v. delivery of $1 \mu\text{g}$ of ACTH), indicating an increased prevalence of subclinical glucocorticoid deficiency in patients receiving imatinib (Bilgir *et al.* 2010). The Food and Drug Administration drug approval summary cautions that although no overt clinically important adrenal suppression has been observed in patients taking sunitinib, subclinical toxicity may be unmasked by physiologic stress; therefore, monitoring for adrenal insufficiency is recommended in patients undergoing stressors such as surgery, trauma, or severe infection (Rock *et al.* 2007).

Glucose metabolism

Increasing evidence suggests that TKIs influence glucose metabolism; both elevated and decreased blood glucose levels have been attributed to TKIs. The mechanism by which TKIs alter blood glucose levels is not known. Of the six FDA-approved TKIs, three of these agents, imatinib, sunitinib, and nilotinib have all been associated with apparently opposite effects on glucose metabolism.

Imatinib has been associated with the adverse reaction of hyperglycemia in 0.1–1% of patients as reported in the adjuvant GIST trial (Novartis). However, a number of reports in the literature have cited glucose-lowering effects thought to be associated with imatinib. A case of regression of long-standing type 2 diabetes during treatment of CML with imatinib was first reported in 2005 (Veneri *et al.* 2005). The authors postulated that inhibition of phosphorylation by imatinib may serve to improve insulin sensitivity. Another report revealed improvement of fasting blood glucose levels in six out of seven diabetic CML patients being treated with imatinib, allowing reduction in insulin dosage or oral antidiabetes therapy (Breccia *et al.* 2004). Two patients with GIST and hypoglycemia were reported, in whom imatinib is likely to have contributed to the severity of the hypoglycemia (Hamberg *et al.* 2006). *In vitro* studies have shown that imatinib enhances β -cell survival, potentially contributing to the glucose-lowering effects observed, thus far with the use of this TKI (Hagerkvist *et al.* 2007).

The prescribing information for sunitinib reports the incidence of hypoglycemia in 73 out of 375 patients (19%) and hyperglycemia in 58 out of 375 patients (15%; Pfizer). Proposed mechanisms include regression of pancreatic islets, modulation of insulin-like growth factor 1 signaling, or decreased glucose uptake. In metastatic renal carcinoma, hyperglycemia has been reported as a toxicity associated with the use

of sunitinib in 15% of cases (Guevremont *et al.* 2009). Blood glucose level variations associated with sunitinib therapy were retrospectively reviewed in 19 diabetic patients treated for RCC. All patients had a decrease in blood glucose level after 4 weeks of treatment (Billemont *et al.* 2008).

Updated data from the phase II trial of nilotinib for patients with CML listed hyperglycemia as a grade $\frac{3}{4}$ toxicity associated with 12% of patients taking this agent (Deremer *et al.* 2008). The prescribing information for nilotinib reports increased blood glucose as a common adverse reaction, occurring in $<5\%$ of patients (Novartis). The increased reports of altered glucose levels in patients receiving TKIs are difficult to interpret, given that some agents are associated with both hyper and hypoglycemia. In diabetic patients, careful assessment of glycemic control while on TKIs is recommended. Monitoring HbA1c and blood glucose levels periodically for nondiabetic patients while on treatment, as well as advising patients to report any excessive thirst or polyuria, are both reasonable recommendations.

Conclusions

Clinicians must be familiar with the recognition and management of endocrine-related side effects associated with TKIs. While an association between TKIs and TSH and parathyroid hormone (PTH) elevation has been established, the etiology behind these associations remains to be elucidated. Both the TSH and TRH receptors are members of the G protein-coupled receptor (GPCR) superfamily, while the thyroid hormone receptor is a nuclear receptor; thus, none of the thyroid signaling pathway receptors belongs to the TK class. The same can be said for the PTH receptor 1, which is yet another GPCR regulating calcium ion homeostasis through the activation of adenylate cyclase and phospholipase C. In addition, the calcium-sensing receptor is another GPCR that acts by sensing extracellular levels of calcium and controls calcium homeostasis by regulating the release of PTH. Although these signaling cascades were once thought to be discrete, recent insights show integrated crosstalk between certain receptor tyrosine kinases (RTK) and GPCRs, whereby these signaling pathways merge to form complex signaling networks (Gavi *et al.* 2006). This ‘cross talk’ may have implications when considering drug side effects. A recent review highlighted the examples of TK activation modifying the function of GPCR (Gavi *et al.* 2006). One prominent example of this ‘cross talk’ is by both the insulin receptor and the β_2 adrenergic receptor, whereby insulin receptor activation promotes the phosphorylation of the β_2 -AR both

directly and indirectly; this well-studied example shows how insulin can counter regulate catecholamine action in the regulation of glucose metabolism. TKs modulate diverse GPCR, and thus impact physiological function. Both the TK and GPCR signaling pathways converge on the MAPK cascade. Crosstalk between these two types of receptors may occur both at the protein–protein interaction level and also downstream in the respective signaling cascades, potentially providing a mechanistic basis for these endocrine-related side effects of TKIs. Further investigation is required to elucidate the exact molecular mechanisms underlying endocrine dysfunction in patients receiving TKIs.

Declaration of interest

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

Funding

Supported by the Intramural Research Division of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Acknowledgements

We would like to thank Nichole Jonas and Jeremy Swan for their assistance with graphic design.

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