Endocrine-metabolic effects of treatment with multikinase inhibitors

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Abstract

Tyrosine kinase inhibitors (TKIs) are emerging as potentially effective options in the treatment of cancer, acting on the pathways involved in growth, avoidance of apoptosis, invasiveness, angiogenesis, and local and distant spread. TKIs induce significant adverse effects, that can negatively affect patients' quality of life. The most common adverse events (AEs) include fatigue, hand–foot skin reaction, decreased appetite, nausea, diarrhoea, hypertension, vomiting, weight loss, endocrinopaties and metabolic disorders.

Patients in therapy with TKIs can develop endocrine-metabolic disorders, including dyslipidemia (~50%), diabetes (~15–40%), and dysthyroidism (~20%). In some cases, patients show an improved glycemia or hypoglycemia. **The effects of TKIs on adrenal or gonadal function are still not completely known. It was shown a higher prevalence of subclinical hypocortisolism in patients treated with imatinib, while an increase of cortisol was reported in patients receiving vandetanib. Long-term treatment with imatinib could impact significantly the ovarian reserve and embryo developmental capacity.**

It is important to evaluate patients, measure glucose levels, and manage hyperglycemia. Mild treatment-related hyperglycemia can be controlled modifying the diet and with exercise, while grade 3 and 4 hyperglycemia can lead to dose reductions and/or oral antihyperglycemic therapy.

Regarding thyroid dysfunctions, it is recommendable to measure the thyroid-stimulating hormone (TSH)/free thyroxine (FT4) levels before starting the therapy, and every 3–4 weeks during the first 6 months as changes in FT4 levels precede the changes in TSH by 3–6 weeks.

Additional studies are necessary to definitely clarify the mechanism of TKIs-induced endocrine-metabolic effects.

Introduction

Cancer is one of the main causes of death. In the past, standard treatments included surgery, radiation therapy and chemotherapy, but in the last 20 years new approaches have been proposed, based on the understanding of the underlying molecular mechanisms (1).

Malignant carcinomas show an autonomous cellular growth related to an imbalance in proliferation/apoptosis, owing to cell signaling pathway alterations. Tyrosine kinases (TKs) are the principal signaling pathway regulators, that catalyze tyrosine residue phosphorylation in various molecules. The altered activation of TKs has been implicated in oncogenesis in different tumors, leading to the idea of tyrosine kinase inhibitors (TKIs) as antitumoral compounds (2).

Thanks to the increased understanding of the molecular pathogenesis of tumors, therapeutic compounds which target certain altered pathways [Rearranged during transfection (RET), BRAF, epidermal growth factor receptor (EGFR), RAS, vascular endothelial growth factor receptor (VEGFR), etc] have been developed (3,4). TKIs compete with the ATP binding sites of the TK catalytic domains, and affect TK dependent oncogenic pathways (3,4), inhibiting the auto-phosphorylation/activation of TKs, preventing the activation of intracellular signaling pathways **(Figure 1)**.

TKIs are specific to one or various homologous TKs, and they are considered multikinase inhibitors (5). By inhibiting only one kinase receptor, other compensatory TKs could be activated, as well as the resistance to TKIs treatment. For this reason, the concurrent inhibition of multiple activated TKs is the best way to act against cancer.

TKIs are emerging as potentially effective options in the treatment of cancer, acting on the above mentioned pathways involved in growth, avoidance of apoptosis, invasiveness, angiogenesis, and local and distant spread (4).

Angiogenesis has a leading role in embryogenesis (6). VEGF contributes to angiogenesis, consisting of VEGF-A, VEGF-B, VEGF-C, VEGF-D, and the placental growth factor, that bind to VEGFR, that comprises VEGFR-1, -2, and -3. VEGFR-1 and VEGFR-2 induction can activate

angiogenesis, while that of VEGFR-3 activates lympho-angiogenesis and embryogenic angiogenesis (7). Furthermore, RET and fibroblast growth factor receptor (FGFR) are TK receptors, important in cancerogenesis (6).

TK receptors are located on cell membranes, and their bond to ligands activate an intracellular phosphorylation cascade, leading to angiogenesis and tumoral growth (6).

Several multitarget TKIs are now approved by US Food and Drug Administration (FDA), and European Medicines Agency (EMA). TKIs are not considered as toxic as cytotoxic chemotherapy, but they can induce significant adverse effects, that can negatively affect patients' quality of life. The most common adverse events (AEs) include fatigue, hand–foot skin reaction, decreased appetite, nausea, diarrhoea, vomiting, hypertension, weight loss, endocrinopaties and metabolic disorders. Therefore, effective AE prevention and management are important to maximize treatment benefits (8,9). In the future, endocrinologists will probably deal with patients with no initial endocrine pathologies, but with endocrinopathy or metabolic disorders caused by antitumoral treatments (1).

This review will take in consideration the endocrine-metabolic side effects derived from the treatment with TKIs.

Endocrine effects of TKIs

According to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, antitumoral therapy side-effects are commonly graded on a 1-to-5 scale (National Cancer Institute 2009): 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death related to AE (even if it is difficult to distinguish between grades 2 and 3, particularly for endocrine side-effects) (10).

Endocrine or metabolic side-effects are rarely grade 3 or 4. Treatment interruption is usually not suggested in hypothyroidism or pituitary deficiency, that are generally managed by hormone replacement therapy. The anticancer regimen can be suspended in severe forms (in particular, thyrotoxicosis). For this reason, AE grading, and the relative measures to be taken, are not

applicable to endocrine side-effects, and molecule withdrawal should be discussed between oncologist and endocrinologist (11).

Pathophysiological mechanisms can be functional (i.e. alteration of hormone transport or insulin secretion, or onset of insulin resistance) or destructive (i.e. dysthyroidism associated with non-autoimmune thyroiditis) (1).

Patients in therapy with TKIs can develop endocrine-metabolic disorders, including dyslipidemia (~50%), diabetes (~15–40%), and dysthyroidism (~20%). In some cases, patients show an improved glycemia or hypoglycemia (11).

Before initiating the treatment with a TKI, thyroid-stimulating hormone (TSH), lipid profile and fasting venous glycemia should be done (11).

Hyperglycemia/Hypoglycemia

Hyperglycemia has systemic effects that can cause constitutional symptoms (i.e. polyuria, dehydration, polydipsia, renal insufficiency, weight loss, unclear vision, anorexia, nausea, fatigue and diarrhea) (12). If untreated, it can lead to life-threatening complications (i.e., cardiovascular disease, neuropathy, nephropathy or kidney failure, retinopathy, etc) and to a progressive worsening of quality of life.

TKIs can influence glucose metabolism through different proposed mechanisms and pathways, and TKIs belonging to the same class can lead both to hypo- or hyperglycemia (13). For example, even if nilotinib, imatinib, and dasatinib are used to treat chronic myeloid leukemia (CML) and target the fusion of the “breakpoint cluster region gene and Abelson murine leukemia” (BCR-ABL) gene, nilotinib can induce hyperglycemia in approximately 40% of patients, while dasatinib and imatinib can cause hypoglycemia (14).

Among the 28 oncological TKIs approved at present by the FDA/EMA, 5 (dabrafenib and trametinib, ceritinib, axitinib, alectinib) can lead to hyperglycemia (15).

TKIs belonging to anaplastic lymphoma kinase (ALK) inhibitors are utilized to treat non-small-cell lung carcinoma (NSCLC), and have distinct effects on glucose. Ceritinib can induce hyperglycemia in about 49% of patients, but not crizotinib (14).

Considering EGFR TKIs targeting T790M, only hyperglycemia has been described, while clinical trials do not report cases of hypoglycemia in patients administered with AZD9291 or rociletinib (13). Preclinical studies reported that hyperglycemia or hyperinsulinemia related to rociletinib could be due to a metabolite which inhibits the type I insulin-like growth factor receptor (IGF-1R) and insulin receptor kinases and, after oral glucose tolerance test, stimulates hyperglycemia in rats (16).

IGF-1R is a cell surface receptor, activating the Ras/MAPK/ERK and PI3K/AKT/mTOR pathways, that control cell growth and inhibit apoptosis. Several IGF-1R inhibitors also block insulin receptor owing to receptor homology (12).

In a phase I/II study, rociletinib was administered to 130 patients with EGFR-mutated NSCLC whose disease had progressed in a preceding therapy with an EGFR inhibitor. Patients with T790M positive disease were administered with rociletinib (500 mg twice daily, 625 mg twice daily, or 750 mg twice daily). The first enrolled 57 patients were treated with the free-base form of rociletinib (150 mg once daily to 900 mg twice daily), and the others with the hydrogen bromide salt (HBr) form (500 mg twice daily to 1000 mg twice daily). The only common dose limiting AE was hyperglycemia (17).

Hyperglycemia has been described with compounds able to inhibit the phosphoinositide 3-kinase (PI3K)-Akt-mammalian target of rapamycin pathway (such as Alpelisib), that affects downstream key insulin signaling pathways through the increase of insulin resistance and the reduction of beta-cell function, similarly to what reported in type 2 diabetes (T2DM) (13).

In rats and mice, the effect of the pan-Akt kinase inhibitor GSK690693 on hyperglycemia has been evaluated, showing raised glucose and insulin levels, and hyperglycemia for approximately 6 hours after the dose. The mechanism at the basis of the hyperglycemia induced by GSK690693 was related to peripheral insulin resistance, raised gluconeogenesis, and/or hepatic glycogenolysis (18).

Multikinase ABL inhibitors (i.e. dasatinib and imatinib) act on glucose metabolism in human beta cells, as demonstrated *in vitro* from chemical-induced apoptosis, activating nuclear factor-kappa B (NF-κB). The inhibitory effect exerted on PDGFR and tumor necrosis factor alpha (TNF-α) can affect the stimulation of beta cell apoptosis and insulin resistance in peripheral tissues (14). Dasatinib and imatinib improve hyperglycemia in patients with previous T2DM.

Other TKIs (including sorafenib, axitinib, sunitinib, pazopanib, ponatinib, and vandetanib) can lead to hypoglycemia (19). A paper retrospectively evaluated blood glucose levels in 17 diabetic and 61 non-diabetic patients treated with different TKIs (20). Mean statistically significant declines of blood glucose levels were: 9 mg/dL with imatinib, 12 mg/dL with sorafenib, 14 mg/dL with sunitinib, and 53 mg/dL with dasatinib. Forty-seven% of the patients with diabetes discontinued their drugs, including insulin in some of them. One diabetic patient in treatment with sunitinib developed symptomatic hypoglycemia. The mechanism at the basis of the hypoglycemic effect of these drugs is still not known, but c-kit and PDGFRβ are the common target kinases of the 4 tested agents (20).

Dyslipidemia

Aggravation or improvement of dyslipidemia are related to different types of TKI, for example imatinib seems to ameliorate lipid profile (21). A paper reported 9 patients with hyperlipidemia and CML, or the hypereosinophilic syndrome, in 8 of whom plasma lipid levels normalized within one month from the beginning of imatinib treatment (at a dose of 400 mg daily) (22). Similar data were shown also by other studies (23,24).

On the contrary, 85/155 patients with metastatic renal cell carcinoma (mRCC) under TKIs (sunitinib, pazopanib, sorafenib, famitinib) showed hyperlipidemia (25). The percentage of patients showing hyperlipidemia with sunitinib, pazopanib, sorafenib and famitinib was 68.1%, 78.6%, 27.5% and 61.9%, respectively. The median progression-free survival (mPFS) and response rate (RR) for patients with normal blood lipids were 8.0 months and 23.9%; 12.9 months and 54.0%

with grade I hyperlipidemia; 14.0 months and 60.7% with grade II hyperlipidemia; 22.2 months and 100.0% with grade III hyperlipidemia; respectively (25).

The plasma lipid profile and global cardiovascular risk were evaluated, before and during nilotinib therapy, in 27 patients with chronic phase (CP)-CML (26). The therapy with nilotinib led to a significant increase of total, low- (LDL) and high-density (HDL) lipoprotein cholesterol within three months, and patients with non-optimal LDL cholesterol raised from 48.1 to 88.9% by 12 months, causing cholesterol-lowering drug intervention in 22.2% of them. The percentage of patients with low HDL cholesterol levels diminished from 40.7 to 7.4% by 12 months. On the other hand, a significant reduction in triglycerides was reported (26). A paper evaluated the incidence of T2DM and hyperlipidemia in patients with CML receiving dasatinib or nilotinib as first- or second-line treatment. Patients administered with nilotinib had a significantly higher incidence of T2DM or hyperlipidemia than patients receiving dasatinib (27). On the contrary, another study in 168 patients with CP-CML treated with imatinib, dasatinib or nilotinib, reported that nilotinib did not induce DM or impaired fasting glucose or metabolic syndrome more extensively than imatinib or dasatinib, even if it worsenes the glycometabolic profile (28).

Imatinib is the first-in-class BCR-ABL TKI used for the treatment of CML, while second- (nilotinib, bosutinib, and dasatinib) and third-generation (ponatinib) TKIs are now present against BCR-ABL mutations, rendering imatinib less effective (29). Scientific evidence shows that imatinib induces low rates of thrombosis, indicating its potential protecting cardiovascular activity in these patients, whereas ponatinib, nilotinib, and dasatinib affect endothelial cells and can lead to atherogenesis increasing vascular permeability. Moreover, nilotinib alters platelet functions and stimulates dyslipidemia and hyperglycemia that can lead to atherosclerosis (29).

Thyroid dysfunctions (TD)

The prevalence of thyroid dysfunctions (TD) (hypo- or hyper-thyroidism) related to a TKI varies considerably according to the type of molecule, the dose administered, the types of thyroid

monitoring, and the recording accuracy of these AEs (30). Moreover, the probability of developing TKI-induced dysthyroidism depends on the patient's background and the existence of an associated thyroid disorder (30,31).

Iatrogenic TD related to TKIs is mainly caused by destructive thyroiditis, probably due to vascular damage (30,32). After a median treatment duration of 6 weeks (1–70 weeks), a thyrotoxic phase is often reported, then hypothyroidism occurs after a median duration of 22 weeks (1–135) (33).

Sunitinib-induced thyroid toxicity has been the most studied clinical model for 10 years. Thyrotoxicosis is reported firstly, then a transient increase in thyroglobulin associated with TKI-induced cell lysis, and hypothyroidism, occur. This is repeated at each cycle when an intermittent on/off pattern is prescribed, and after several cycles of treatment, a reduced vascularization of the thyroid parenchyma is shown with hypotrophy of the gland that could be responsible for permanent hypothyroidism if the therapy is prolonged (30). During the thyrotoxicosis phase, TSH is low and FT4 is increased (or into the normal range, in subclinical hyperthyroidism), TSH receptor autoantibodies (TRAb) are often absent and are measured only if a suspect of Graves' disease (GD) is present (30).

A meta-analysis evaluated 12 clinical trials (6 with sunitinib, 4 with cediranib and 2 with axitinib), after the exclusion of ineligible studies. Patients administered with these drugs had a significantly higher risk of all-grade hypothyroidism with a relative risk of 3.59 (95% CI = 2.40–5.38, $P \leq 0.0001$) (33).

Hyperthyroidism affects an average of 15.8% of patients undergoing TKI therapy (33,34) and corresponds rather to a state of transient, most often subclinical, thyrotoxicosis. The occurrence of hypothyroidism is late and prolonged, easy to be recognized and therefore reported more frequently (18% of patients), and it can persist also when the therapy is discontinued (35).

Hypothyroidism ***(Table 1)***

Hypothyroidism is the most frequent TKIs-induced thyroid dysfunction (34,36), and different TKIs (including sunitinib, sorafenib, cabozantinib, vandetanib, lenvatinib) are responsible for inducing it (34,37). TKIs can promote hypothyroidism through several mechanisms, such as ischemic thyroiditis due to a marked capillary regression caused by blocking VEGF, higher thyroid hormone (TH) metabolism, inhibition of iodine organification, inhibition of peroxidase, blocking of iodine uptake, thyroid autoimmunity, and alteration of the intestinal absorption and of the enterohepatic reabsorption of levothyroxine. Around 30-35% of patients treated with TKIs have a transient increase of TSH levels, without any need of treatment (37).

An incidence analysis was conducted considering 6678 patients administered with sunitinib from 24 eligible trials (31). All-grade hypothyroidism had an incidence of 9.8% (95% CI 7.3-12.4%), and high-grade of 0.4% (95% CI 0.3-0.5%). A meta-analysis of 2787 subjects in 7 randomized trials reported a RR of all- and high-grade hypothyroidism of 13.95 (95% CI 6.91-28.15; $P < 0.00001$) and 4.78 (95% CI 1.09-20.84; $P = 0.04$), respectively. A subgroup analysis in patients treated with sunitinib for a longer period of time ($P = 0.02$) reported a significantly increased incidence of all-grade hypothyroidism (31).

A paper reported the data from a global, expanded-access trial in 4543 patients with mRCC, who were administered with oral sunitinib, 50 mg per day on a 4-weeks-on-2-weeks-off schedule. All-grade hypothyroidism was shown as a treatment-related AE in 11% of patients (38).

A prospective study investigated sunitinib in Japanese patients with mRCC, with an initial oral dose of 50 mg/day on a 4-weeks-on and 2-weeks-off schedule. The mPFS was 22.7 weeks, grade ≥3 AEs occurred in 70%, with hypothyroidism in 593/1671 (35.5%) (39).

Another study investigated the effect of sunitinib in a non-screened group of patients with mRCC. The frequency of induced hypothyroidism was 43% (40).

A meta-analysis of 500 patients with mRCC in 11 retrospective and prospective studies, treated with sunitinib or sorafenib, did not report a significant difference in PFS between patients who developed hypothyroidism during sunitinib and those who did not (41).

A phase III, open-label, multicentre trial (ClinicalTrials.gov, number NCT01761266), still active, but not recruiting, is conducted in patients with unresectable HCC (42). Patients received oral lenvatinib (for bodyweight <60 kg, 8 mg/day; for bodyweight ≥60 kg, 12 mg/day), or sorafenib (400 mg twice-daily in 28-day cycles). The eligible 954/1492 patients received randomly sorafenib (n=476) or lenvatinib (n=478). Hypothyroidism of any grade was present in 16% of patients receiving lenvatinib and 2% in those receiving sorafenib (42).

In phase III studies of vandetanib and cabozantinib, about 90% of patients have prior thyroidectomy, and 49% of those treated with vandetanib and 57% with cabozantinib have elevated TSH levels and require an increase in thyroid replacement therapy (43).

A paper evaluated the data about TSH, free thyroxine (FT4), and levothyroxine in adolescents and children with medullary thyroid cancer (MTC) involved in phase I/II trials of vandetanib (44). Thirteen patients with multiple endocrine neoplasia type 2B (MEN 2B) and MTC were screened, and among them, 11 (85%) had been previously submitted to thyroidectomy, and all were administered with single-drug treatment with vandetanib for more than 6 months. The 11 athyreotic patients had significantly raised TSH levels, while FT4 remained into the normal range, and the levothyroxine dose was increased from 91 mcg/m(2)/day (±24) to 116 mcg/m(2)/day (±24). In the 2 patients not previously thyroidectomized, FT4 and TSH remained normal in the follow-up (44).

The effect of cabozantinib has been evaluated in 17 patients with advanced nonclear cell RCC, administered with the dose of 60 mg once a day in 28 days cycles, and dose reductions to 40 or 20 mg were necessary owing to toxicities. The frequency of induced hypothyroidism was 24% (45).

A prospective, phase II trial enrolled patients with platinum-failure, recurrent/metastatic Merkel cell carcinoma (MCC) who received oral cabozantinib 60 mg daily until disease progression (46). Eight patients were accrued, then the study was closed prematurely owing to toxicity and lack of responses. Four/8 patients (50%) had hypothyroidism (46).

The randomised phase II CABOSUN trial compared sunitinib with cabozantinib in patients with advanced RCC randomised 1:1 to sunitinib 50 mg daily (4 weeks on/2 weeks off) or cabozantinib

60 mg daily. Eighteen/78 (23%) patients receiving cabozantinib developed hypothyroidism, and 4/72 (6%) treated with sunitinib (47).

A study evaluated 59 patients with unresectable progressive MTC administered with lenvatinib (24-mg daily, 28-day cycles) until unmanageable toxicity, disease progression, interruption, or death. Twelve/59 (20%) patients had an increase in blood TSH levels (48). In another study (ClinicalTrials.gov, number NCT00946153), patients with histologically/clinically confirmed advanced HCC, who were not submitted to surgical resection or local treatments, were administered with lenvatinib 12 mg once daily in 28-day cycles. All 46 patients experienced at least one AE, and hypothyroidism was present in 10/46 (21.7%) (49). Furthermore, a retrospective study investigated lenvatinib (24 mg once daily) in 5 patients with ATC and 4/5 patients (80%) showed hypothyroidism of any grade (50).

Hyperthyroidism ***(Table 2)***

A paper reviewed the published literature on TKI-induced TD, to evaluate the AEs of targeted therapy on thyroid function in oncological patients, and the impact of TD on disease prognosis (51). Twenty-two original studies and 1641 patients were included. TD is a common AE of TKIs as, among the 1641 included patients, 751 (45.8%) developed TD. Hypothyroidism was shown in 545 (33.2%) patients. The patients who were tested (n=1498) and developed hyperthyroidism were 47/1498 patients (3.14%) (51).

The case of a 57-year-old man with lumbar chordoma receiving 800 mg sorafenib daily has been reported (52). Upon 18 weeks of therapy, the patient developed hyperthyroidism with positive TRAb, even if pre-treatment TSH was normal. Moreover, GD recurred during treatment with imatinib. The fact that GD occurred after two different TKIs indicates that it could be a rare but important class effect (52).

A study investigated the incidence and clinical course of thyrotoxicosis in patients with metastatic mRCC treated with sunitinib. Among the 62 enrolled patients, thyrotoxicosis preceded hypothyroidism in 2 (3.2%) (53).

A study evaluated thyroid function in patients enrolled in two phase II clinical trials (54). Thirty-three patients received cabozantinib for metastatic bladder cancer and metastatic soft tissue sarcoma, and follow-up thyroid function tests were available for 31, reporting TD in 93.1% of patients, with a preponderance of subclinical hypothyroidism. Two patients had a transient thyrotoxicosis, and then hypothyroidism (54).

Adrenal dysfunctions

The effects of TKIs on adrenal function are still not completely known. In patients treated with imatinib, a higher prevalence of subclinical hypocortisolism was shown (55), while an increase of cortisol was reported in 14 patients receiving vandetanib (56).

A study assessed the basal and stimulated adrenal function in 12 patients with advanced radioiodine refractory differentiated thyroid cancer (DTC) and MTC, receiving, respectively, lenvatinib or vandetanib. Ten patients with fatigue had a gradual adrenocorticotropic hormone (ACTH) increase and normal cortisol levels, and 6 of them had a cortisol response upon ACTH stimulation, in agreement with the diagnosis of primary adrenal insufficiency (PAI). Patients with PAI were treated with cortisone acetate replacement treatment, and fatigue improved, as estimated by the CTCAE version 4.03, indicating that PAI can induce fatigue during the therapy with lenvatinib and vandetanib (57).

Gonadal effects

Spermatogenesis

The possible effect of TKIs on spermatogenesis could be due to a direct action exercised on meiosis (58). For example, the c-abl TKs, primary target of imatinib and dasatinib, appear to be involved in

meiosis I of spermatogenesis, and C-kit (target of nilotinib, sunitinib, imatinib, and dasatinib) is thought to be implicated in turning on the differentiation process of spermatogenesis. TKIs may also affect function, such as fertilization and sperm motility. Capacitation is the phenomenon through which spermatozoon achieves fertilizing capacity upon the exposition to the female reproductive tract, that has hormones and signal molecules that are necessary to increase sperm cell motility. After capacitation, a sperm cell is hyperactivated, leading to the acrosome reaction and subsequent fertilization. TKIs that target these sperm TKs could significantly affect capacitation, negatively impacting sperm membrane potential, sperm cell motility, and hyperactivation (58).

The effects of dasatinib, nilotinib, and imatinib in men with CML have been evaluated before and after 4 months from the beginning of TKI therapy. Serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels significantly decreased, such as sperm motility, total sperm, and the percentage with normal morphology (59). Dasatinib had a minor effect on count, volume, motility, and morphology of sperm in comparison to nilotinib and imatinib. However, studies in humans did not show effects of TKIs on male fertility (60).

Hypogonadism

Crizotinib, a competitive inhibitor of ALK and c-Met kinase, has shown notable effectiveness in ALK-positive NSCLC. A strong decrease in testosterone is reported within days from the beginning of crizotinib, even according to dose interruptions and restart of therapy. LH and FSH decreased in some patients, indicating crizotinib has a central (hypothalamic or pituitary) effect, while in others LH and FSH remained in the normal range or elevated, supporting the idea that crizotinib has also a further direct gonadal effect (61).

A study evaluated the variation of testosterone in 19 patients with NSCLC treated, and 19 not treated, with crizotinib. Total testosterone was low (<241 ng/dL) in 19/19 (100%) men treated with crizotinib, and in 6/19 patients (32%) with metastatic NSCLC not administered with crizotinib ($P = 0.0002$). The beginning of crizotinib in 2 patients, who had earlier normal testosterone levels, led to

a prompt decrease in testosterone, LH and FSH within 14-21 days. The interruption of therapy led back to normal testosterone levels. The reported data suggested that crizotinib can cause a rapid reduction of testosterone in male patients. A central effect was supposed, but further direct effects on testis may not be excluded (62).

Another study was conducted in 41 males with mRCC treated with pazopanib, sunitinib, and axitinib. The incidence of hypogonadism was 77%; odds ratio for hypogonadism at >30 months on TKIs was 12.1 ($P = 0.011$), and the odds ratios above and below this value had a confirmatory trend, indicating that this could be a chronic AE (63).

Infertility

The kinase signaling pathways targeted by TKIs are crucial for the formation, maturation and survival of oocytes and follicles, and for this reason an association between therapy and ovarian insufficiency is possible. The c-Kit and its ligand Kit-L are crucial to establish primordial follicle activation, primordial germ cells, growth and survival of oocytes and granulosa cell proliferation. PDGFR and its ligand are determinant in the initial activation of follicles and may be implicated in angiogenesis during the formation of corpus luteum. Moreover, oocytes and somatic cells strongly express VEGF, and VEGF/VEGFR system is involved in the process of selection and luteinisation of follicles and maintenance of function of the corpus luteum (64).

A study evaluated ovarian toxicity of sunitinib in 6-weeks old female mice treated for 5 weeks, once daily, with sunitinib (50 mg/kg/d) or vehicle alone. Sunitinib treatment significantly decreased corpora lutea number/ovary ($P < 0.01$) and serum Anti Mullerian hormone (belonging to TGFβ family, that is expressed in granulosa cells of preantral and small antral follicles and can be a good marker of the amount of growing follicles) levels in comparison to control mice ($P < 0.05$), whereas primordial and growing follicles numbers *per* ovary did not differ in the two groups. Upon treatment interruption, all female mice could have litters (64).

The effect of long-term imatinib was evaluated on follicle development and embryo quality, in adult female mice receiving daily intraperitoneal injections of this drug for 4–6 weeks. The treatment led to a shift in follicle development, and fewer primordial follicles, but higher primary and secondary follicles ($P < 0.05$), while no effects on fertilization rates or ovulation were reported. Blastocysts obtained from females receiving imatinib had fewer total cells ($P < 0.05$), and a significant shift from inner cell mass to increased trophectoderm cells. These data indicated that long-term treatment with this TKI could impact significantly the ovarian reserve and embryo developmental capacity (65).

Effects on the hypothalamic-pituitary-thyroid axis

The treatment with TKIs can cause derangements in the hypothalamic-pituitary-thyroid axis, perhaps through the direct inhibition of thyroid hormone feedback at pituitary or hypothalamic level, increasing TSH and the need of higher levothyroxine replacement doses in thyroidectomized patients. Axitinib, and with a lower extent, also sunitinib or sorafenib, is associated with elevated TSH levels (66).

Management of endocrine effects of treatment with TKIs

Hyperglycemia can lead to life-threatening complications and affect negatively the patient quality of life causing dose reductions or discontinuations. For these reasons, it is important to evaluate patients, measure glucose levels, and manage hyperglycemia (13). In real-world clinical data, patients needing anticancer therapy can have glucose intolerance, and previous or undiagnosed diabetes. For this reason, evaluating patients for those conditions can suggest which of them would need close monitoring, and even those considered low risk can still develop hyperglycemia (12). During the therapy, patients can be evaluated for hyperglycemia [by measuring fasting and/or postprandial blood glucose levels (in patients with an already diagnosed diabetes) and periodic hemoglobin A1c testing] and for insulin resistance (by insulin levels). Mild treatment-related

hyperglycemia can be controlled modifying the diet and with exercise, while grade 3 and 4 hyperglycemia can lead to dose reductions and/or oral antihyperglycemic therapy (categorized by mechanisms; for insulin receptor/IGF-1R inhibitors, insulin sensitizers (such as metformin) or a sodium/glucose cotransporter 2 (SGLT2) inhibitor; or others, such as insulin sensitizer, secretagogues, an SGLT2 inhibitor, or insulin) (12,15).

Diagnosis of dyslipidemia during TKIs treatment is not different from that of non-iatrogenic dyslipidemia and the target levels are selected according to the general health status, prognosis, cardiovascular history and risk factors (21). The lipid profile should be monitored beside the thyroidal profile, since TKIs can lead to hypothyroidism, that is responsible to impair the former. At present, guidelines can be applied in case of good oncologic prognosis (67).

A history of thyroid disorders does not contraindicate initiation of TKIs, and the screening for anti-thyroid autoimmunity (anti-thyroperoxidase antibodies, anti-thyroglobulin antibodies, TRAbs) before initiation of the treatment is not recommended (30). It is recommendable to measure the TSH/FT4 levels before starting the therapy, and every 3–4 weeks during the first 6 months as changes in FT4 levels precede the changes in TSH by 3–6 weeks. The occurrence of TDs, usually grade 1 or 2, does not contraindicate the continuation of TKIs (30).

In case of thyrotoxicosis, a symptomatic treatment can be initiated including low-dose non-cardioselective β-blockers, such as propranolol, in the absence of contraindication, to control cardiothyrosis and tremors. Corticosteroids are used in the case of Graves' ophthalmopathy (30). Considering the risk of progression to hypothyroidism after thyrotoxicosis, the regular monitoring of TSH and FT4 is necessary. Hyperthyroidism can be solved, followed or not by hypothyroidism. During hypothyroidism, the β-blocker treatment is discontinued and a supportive treatment with levothyroxine can be started (30).

Conclusion

Cancer standard treatments include surgery, radiation therapy and chemotherapy, but in the last 20 years new approaches have been evaluated, based on the understanding of the underlying molecular mechanisms (1).

Various multitarget TKIs are approved by US FDA, and EMA. TKIs are not considered as toxic as cytotoxic chemotherapy, but they can lead to significant adverse effects, that can negatively affect patients' quality of life. The most common AEs include fatigue, hand–foot skin reaction, decreased appetite, nausea, vomiting, diarrhoea, hypertension, weight loss, endocrinopaties and metabolic disorders.

Patients in therapy with TKIs can develop endocrine-metabolic disorders, including dyslipidemia (~50%), diabetes (~15–40%), and dysthyroidism (~20%). In some cases, patients show an improved glycemia or hypoglycemia (11).

It is important to evaluate patients, measure glucose levels, and manage hyperglycemia. During the therapy, patients can be screened for hyperglycemia [by measuring fasting and/or postprandial blood glucose levels (in patients with an already diagnosed diabetes) and periodic hemoglobin A1c testing]. Mild treatment-related hyperglycemia can be controlled modifying the diet and with exercise, while grade 3 and 4 hyperglycemia can lead to dose reductions and/or oral antihyperglycemic therapy (12). The diagnosis of dyslipidemia during TKIs treatment is not different from that of non-iatrogenic dyslipidemia and the lipid profile should be assessed beside the thyroidal profile, since TKIs can lead to hypothyroidism, that is responsible to impair the former.

Regarding TDs, it is recommendable to measure the TSH/FT4 levels before starting the therapy, and every 3–4 weeks during the first 6 months as changes in FT4 levels precede the changes in TSH by 3–6 weeks. The occurrence of TDs, usually grade 1 or 2, does not contraindicate the continuation of TKIs (30).

Additional studies are necessary to definitely clarify the mechanism of TKIs-induced endocrine-metabolic effects.

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References

1. Castinetti F & Borson-Chazot F. Introduction to expert opinion on endocrine complications of new anticancer therapies. *Annales d'endocrinologie* (Paris) 2018 **79** 535–538.

2. Croce CM. Oncogenes and cancer. *The New England journal of medicine* 2008 **358** 502–511.

3. Ferrari SM, Fallahi P, Politti U, Materazzi G, Baldini E, Ulisse S, Miccoli P & Antonelli A. Molecular Targeted Therapies of Aggressive Thyroid Cancer. *Frontiers in endocrinology* (Lausanne) 2015 **6** 176.

4. Fallahi P, Mazzi V, Vita R, Ferrari SM, Materazzi G, Galleri D, Benvenga S, Miccoli P & Antonelli A. New therapies for dedifferentiated papillary thyroid cancer. *International journal of molecular sciences* 2015 **16** 6153–6182.

5. Sarlis NJ & Benvenga S. Molecular signaling in thyroid cancer. *Cancer treatment and research* 2004 **122** 237–64.

6. Ancker OV, Krüger M, Wehland M, Infanger M & Grimm D. Multikinase Inhibitor Treatment in Thyroid Cancer. *International journal of molecular sciences* 2019 **21** 10.

7. Shibuya M & Claesson-Welsh L. Signal transduction by vegf receptors in regulation of angiogenesis and lymphangiogenesis. *Experimental cell research* 2006 **312** 549–560.

8. Rimassa L, Danesi R, Pressiani T & Merle P. Management of adverse events associated with tyrosine kinase inhibitors: Improving outcomes for patients with hepatocellular carcinoma. *Cancer treatment reviews* 2019 **77** 20–28.

9. Galetta F, Franzoni F, Bernini G, Fallahi P, Carpi A, Cini G, Tocchini L, Antonelli A & Santoro G. Cardiovascular complications in patients with pheochromocytoma: a mini-review. *Biomedicine & pharmacotherapy* 2010 **64** 505–509.

10. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

11. Castinetti F, Albarel F, Archambeaud F, Bertherat J, Bouillet B, Buffier P, Briet C, Cariou B, Caron P, Chabre O, et al. Endocrine side-effects of new anticancer therapies: Overall monitoring and conclusions. *Annales d'endocrinologie* (Paris) 2018 **79** 591–595.

12. Goldman JW, Mendenhall MA & Rettinger SR. Hyperglycemia Associated With Targeted Oncologic Treatment: Mechanisms and Management. *Oncologist* 2016 **21** 1326–1336.

13. Villadolid J, Ersek JL, Fong MK, Sirianno L & Story ES. Management of hyperglycemia from epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) targeting T790M-mediated resistance. *Translational lung cancer research* **2015** 4 576–583.

14. Deangelo DJ. Managing chronic myeloid leukemia patients intolerant to tyrosine kinase inhibitor therapy. *Blood cancer journal* 2012 **2** e95.

15. Shah RR. Hyperglycaemia Induced by Novel Anticancer Agents: An Undesirable Complication or a Potential Therapeutic Opportunity? *Drug safety* 2017 **40** 211-228.

16. Sequist LV, Soria JC, Goldman JW, Wakelee HA, Gadgeel SM, Varga A, Papadimitrakopoulou V, Solomon BJ, Oxnard GR, Dziadziuszko R, et al. Rociletinib in EGFR-mutated non-small-cell lung cancer. *The New England journal of medicine* 2015 **372** 1700–1709.

17. Sequist LV, Goldman JW, Wakelee HA, Camidge DR, Yu HA, Varga A, Solomon B, Oxnard GR, Ou SHI, Papadimitrakopoulou V, et al. Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts). *Journal of Clinical Oncology* 2015 **33** 8001.

18. Crouthamel MC, Kahana JA, Korenchuk S, Zhang SY, Sundaresan G, Eberwein DJ, Brown KK, Kumar R. Mechanism and management of AKT inhibitor-induced hyperglycemia. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2009 **15** 217–225.

19. Dy GK & Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA: a cancer journal for clinicians* 2013 **63** 249–279.

20. Agostino NM, Chinchilli VM, Lynch CJ, Koszyk-Szewczyk A, Gingrich R, Sivik J, Drabick JJ. Effect of the tyrosine kinase inhibitors (sunitinib, sorafenib, dasatinib, and imatinib) on blood glucose levels in diabetic and nondiabetic patients in general clinical practice. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners* 2011 **17** 197–202

21. Buffier P, Bouillet B, Smati S, Archambeaud F, Cariou B & Verges B. Expert opinion on the metabolic complications of new anticancer therapies: Tyrosine kinase inhibitors. *Annales d'endocrinologie* 2018 **79** 574–582.

22. Gottardi M, Manzato E & Gherlinzoni F. Imatinib and hyperlipidemia. *The New England journal of medicine* 2005 **353** 2722–2723.

23. Franceschino A, Tornaghi L, Benemacher V, Assouline S & Gambacorti-Passerini C. Alterations in creatine kinase, phosphate and lipid values inpatients with chronic myeloid leukemia during treatment with imatinib. *Haematologica* 2008 **93** 317–318.

24. Gologan R, Constantinescu G, Georgescu D, Ostroveanu D, Vasilache D, Dobrea C, Iancu D & Popov V. Hypolipemiant besides antileukemic effect of imatinib mesylate. *Leukemia research* 2009 **33** 1285–1287.

25. Song Y, Du C, Zhang W, Sun Y, Yang L, Cui C, Chi Y, Shou J, Zhou A, Wang J, et al. A study on the association between hyperlipidemia and hypothyroidism and the response to TKIs in metastatic renal cell carcinoma. *Asia-Pacific journal of clinical oncology* 2016 **12** 174–180.

26. Rea D, Mirault T, Cluzeau T, Gautier JF, Guilhot F, Dombret H & Messas E. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. *Haematologica* 2014 **99** 1197–1203.

27. Franklin M, Burns L, Perez S, Yerragolam D & Makenbaeva D. Incidence of type 2 diabetes mellitus and hyperlipidemia in patients prescribed dasatinib or nilotinib as first- or second-line therapy for chronic myelogenous leukemia in the US. *Current medical research and opinion* 2018 **34** 353–360.

28. Iurlo A, Orsi E, Cattaneo D, Resi V, Bucelli C, Orofino N, Sciumè M, Elena C, Grancini V, Consonni D, et al. Effects of first- and second-generation tyrosine kinase inhibitor therapy on glucose and lipid metabolism in chronic myeloid leukemia patients: a real clinical problem? *Oncotarget* 2015 **6** 33944–33951.

29. Haguet H, Douxfils J, Chatelain C, Graux C, Mullier F & Dogné JM. BCR-ABL Tyrosine Kinase Inhibitors: Which Mechanism(s) May Explain the Risk of Thrombosis?. *TH open:companion journal to thrombosis and haemostasis* 2018 **2** e68─e88.

30. Jannin A, Penel N, Ladsous M, Vantyghem MC & Do Cao C. Tyrosine kinase inhibitors and immune checkpoint inhibitors-induced thyroid disorders. *Critical reviews in oncology/hematology* 2019 **141** 23─35.

31. Funakoshi T & Shimada YJ. Risk of hypothyroidism in patients with cancer treated with sunitinib: a systematic review and meta-analysis. *Acta oncologica* 2013 **52** 691–702.

32. Alexandraki KI, Daskalakis K, Tsoli M, Grossman AB & Kaltsas GA. Endocrinological Toxicity Secondary to Treatment of Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs). *Trends in endocrinology and metabolism:TEM* 2020 **31** 239─255.

33. Abdel-Rahman O & Fouad M. Risk of thyroid dysfunction in patients with solid tumors treated with VEGF receptor tyrosine kinase inhibitors: a critical literature review and meta analysis. *Expert review of anticancer therapy* 2014 **14** 1063–1073.

34. Fallahi P, Ferrari SM, Vita R, Di Domenicantonio A, Corrado A, Benvenga S & Antonelli A. Thyroid dysfunctions induced by tyrosine kinase inhibitors. *Expert opinion on drug safety* 2014 **13** 723─733.

35. Beukhof CM, van Doorn L, Visser TJ, Bins S, Visser WE, van Heerebeek R, van Kemenade FJ, de Rijke YB, de Herder WW, Chaker L, et al. Sorafenib-induced changes in thyroid hormone levels in patients treated for hepatocellular carcinoma. *The Journal of clinical endocrinology and metabolism* 2017 **102** 2922–2929.

36. Galetta F, Franzoni F, Fallahi P, Tocchini L, Braccini L, Santoro G & Antonelli A. Changes in heart rate variability and QT dispersion in patients with overt hypothyroidism. *European journal of endocrinology* 2008 **158** 85–90.

37. Rizzo LFL, Mana DL & Serra HA. Drug-induced hypothyroidism. *Medicina* 2017 **77** 394–404.

38. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, Lee SH, Haanen J, Castellano D, Vrdoljak E, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. *British journal of cancer* 2015 **113** 12–19.

39. Akaza H, Naito S, Ueno N, Aoki K, Houzawa H, Pitman Lowenthal S & Lee SY. Real-world use of sunitinib in Japanese patients with advanced renal cell carcinoma: efficacy, safety and biomarker analyses in 1689 consecutive patients. *Japanese journal of clinical oncology* 2015 **45** 576–583.

40. Coelho RC, Reinert T, Campos F, Peixoto FA, de Andrade CA, Castro T & Herchenhorn D. Sunitinib treatment in patients with advanced renal cell cancer: the Brazilian National Cancer Institute (INCA) experience. *International braz j urol : official journal of the Brazilian Society of Urology* 2016 **42** 694–703.

41. Nearchou A, Valachis A, Lind P, Akre O & Sandström P. Acquired hypothyroidism as a predictive marker of outcome in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors: A literature-based meta-analysis. *Clinical genitourinary cancer* 2015 **13** 280–286.

42. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018 **391** 1163–1173.

43. Brose MS, Bible KC, Chow LQM, Gilbert J, Grande C, Worden F & Haddad R. Management of treatment-related toxicities in advanced medullary thyroid cancer. *Cancer treatment reviews* 2018 **66** 64–73.

44. Lodish M, Gkourogianni A, Bornstein E, Sinaii N, Fox E, Chuk M, Marcus L, Akshintala S, Balis F, Widemann B, et al. Patterns of thyroid hormone levels in pediatric medullary thyroid

carcinoma patients on vandetanib therapy. *International journal of pediatric endocrinology* 2015 **2015** 3.

45. Prisciandaro M, Ratta R, Massari F, Fornarini G, Caponnetto S, Iacovelli R, De Giorgi U, Facchini G, Scagliarini S, Sabbatini R, et al. Safety and Efficacy of Cabozantinib for Metastatic Nonclear Renal Cell Carcinoma: Real-world Data From an Italian Managed Access Program. *American journal of clinical oncology* 2019 **42** 42–45.

46. Rabinowits G, Lezcano C, Catalano PJ, McHugh P, Becker H, Reilly MM, Huang J, Tyagi A, Thakuria M, Bresler SC, et al. Cabozantinib in Patients with Advanced Merkel Cell Carcinoma. *The oncologist* 2018 **23** 814–821.

47. Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, Walsh M, Olencki T, Picus J, Small EJ, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. *European journal of cancer* 2018 **94** 115–125.

48. Schlumberger M, Jarzab B, Cabanillas ME, Robinson B, Pacini F, Ball DW, McCaffrey J, Newbold K, Allison R, Martins RG, et al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer. *Clinical cancer research:an official journal of the American Association for Cancer Research* 2016 **22** 44–53.

49. Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, Tamai T, Suzuki T, Hisai T, Hayato S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *Journal of gastroenterology* 2017 **52** 512–519.

50. Koyama S, Miyake N, Fujiwara K, Morisaki T, Fukuhara T, Kitano H & Takeuchi H. Lenvatinib for Anaplastic Thyroid Cancer and Lenvatinib-Induced Thyroid Dysfunction. *European thyroid journal* 2018 **7** 139–144.

51. Gabora K, Piciu A, Bădulescu IC, Larg MI, Stoian IA & Piciu D. Current evidence on thyroid related adverse events in patients treated with protein tyrosine kinase inhibitors. *Drug metabolism reviews* 2019 **51** 562–569.

52. Eroukhmanoff J, Castinetti F, Penel N & Salas S. Auto-immune thyroid dysfunction induced by tyrosine kinase inhibitors in a patient with recurrent chordoma. *BMC Cancer* 2016 **16** 679.

53. Jazvić M, Prpić M, Jukić T, Murgić J, Jakšić B, Kust D, Prgomet A, Bolanča A & Kusić Z. Sunitinib-induced thyrotoxicosis - a not so rare entity. *Anticancer research* 2015 **35** 481–485.

54. Yavuz S, Apolo AB, Kummar S, del Rivero J, Madan RA, Shawker T, Reynolds J & Celi FS. Cabozantinib-induced thyroid dysfunction: a review of two ongoing trials for metastatic bladder cancer and sarcoma. *Thyroid* 2014 **24** 1223–1231.

55. Bilgir O, Kebapcilar L, Bilgir F, Sarì I, Oner P, Karaca B & Alacacioglu I. Is there any relationship between imatinib mesylate medication and hypothalamic-pituitary-adrenal axis dysfunction? *International journal of clinical practice* 2010 **64** 45–50.

56. Brassard M, Neraud B, Trabado S, Salenave S, Brailly-Tabard S, Borget I, Baudin E, Leboulleux S, Chanson P, Schlumberger M, et al. Endocrine effects of the tyrosine kinase inhibitor vandetanib in patients treated for thyroid cancer. *The Journal of clinical endocrinology and metabolism* 2011 **96** 2741–2749.

57. Colombo C, De Leo S, Di Stefano M, Vannucchi G, Persani L & Fugazzola L. Primary Adrenal Insufficiency During Lenvatinib or Vandetanib and Improvement of Fatigue After Cortisone Acetate Therapy. *The Journal of clinical endocrinology and metabolism* 2019 **104** 779–784.

58. Ramstein JJ, Tsai KK & Smith JF. Tyrosine Kinase Inhibitors and Male Reproductive Health. *Clinical pharmacology and therapeutics* 2017 **102** 754–756.

59. Yassin MA, Soliman AT, Elawa AS, El-Ayoubi HR & Desanctis V. Effects of tyrosine kinase inhibitors on spermatogenesis and pituitary gonadal axis in males with chronic myeloid leukemia. *Blood (ASH Annual Meeting Abstracts)* 2012 **120** Abstract 1688.

60. Berman E, Druker BJ & Burwick R. Chronic Myelogenous Leukemia: Pregnancy in the Era of Stopping Tyrosine Kinase Inhibitor Therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2018 **36** 1250–1256.

61. Pender A & Popat S. The efficacy of crizotinib in patients with ALK-positive nonsmall cell lung cancer. *Therapeutic advances in respiratory disease* 2015 **9** 97–104.

62. Weickhardt AJ, Rothman MS, Salian-Mehta S, Kiseljak-Vassiliades K, Oton AB, Doebele RC, Wierman ME & Camidge DR. Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic nonsmall cell lung cancer. *Cancer* 2012 **118** 5302–5309.

63. Afshar M, Patel HRH, Jain A, Kumar A, Patel P, James ND & Porfiri E. Chronic tyrosine kinase inhibitor (TKI) use in metastatic renal cell carcinoma (mRCC): can this lead to the adverse effect of hypogonadism?. *Expert review of anticancer therapy* 2019 **19** 529–532.

64. Bernard V, Bouilly J, Kramer P, Carré N, Schlumberger M, Visser JA, Young J & Binart N. The Tyrosine Kinase Inhibitor Sunitinib Affects Ovulation but Not Ovarian Reserve in Mouse: A Preclinical Study. *PLoS One* 2016 **11** e0152872.

65. Salem W, Ho JR, Woo I, Ingles SA, Chung K, Paulson RJ & McGinnis LK. Long-term imatinib diminishes ovarian reserve and impacts embryo quality. *Journal of assisted reproduction and genetics* 2020 **37** 1459–1466.

66. Zatelli MC, Ambrosio MR, Bondanelli M & Degli Uberti E. Pituitary side effects of old and new drugs. *Journal of endocrinological investigation* 2014 **37** 917–923.

67. French Society of Endocrinology (SFE), Francophone Society of Diabetes (SFD), New French Society of Atherosclerosis (NSFA), Béliard S, Bonnet F, Bouhanick B, Bruckert E, Cariou B, Charrière S, Durlach V, et al. Consensus statement on the management of dyslipidaemias in adults. *Annales d'endocrinologie* 2017 **78** 43–53.

Figure Legend

Figure 1. Multikinase inhibitors exercise inhibitory effects on several pathways. TKIs compete with the ATP binding sites of the TK catalytic domains, and affect TK dependent oncogenic pathways, inhibiting the auto-phosphorylation/activation of TKs, hindering the activation of intracellular signaling pathways.

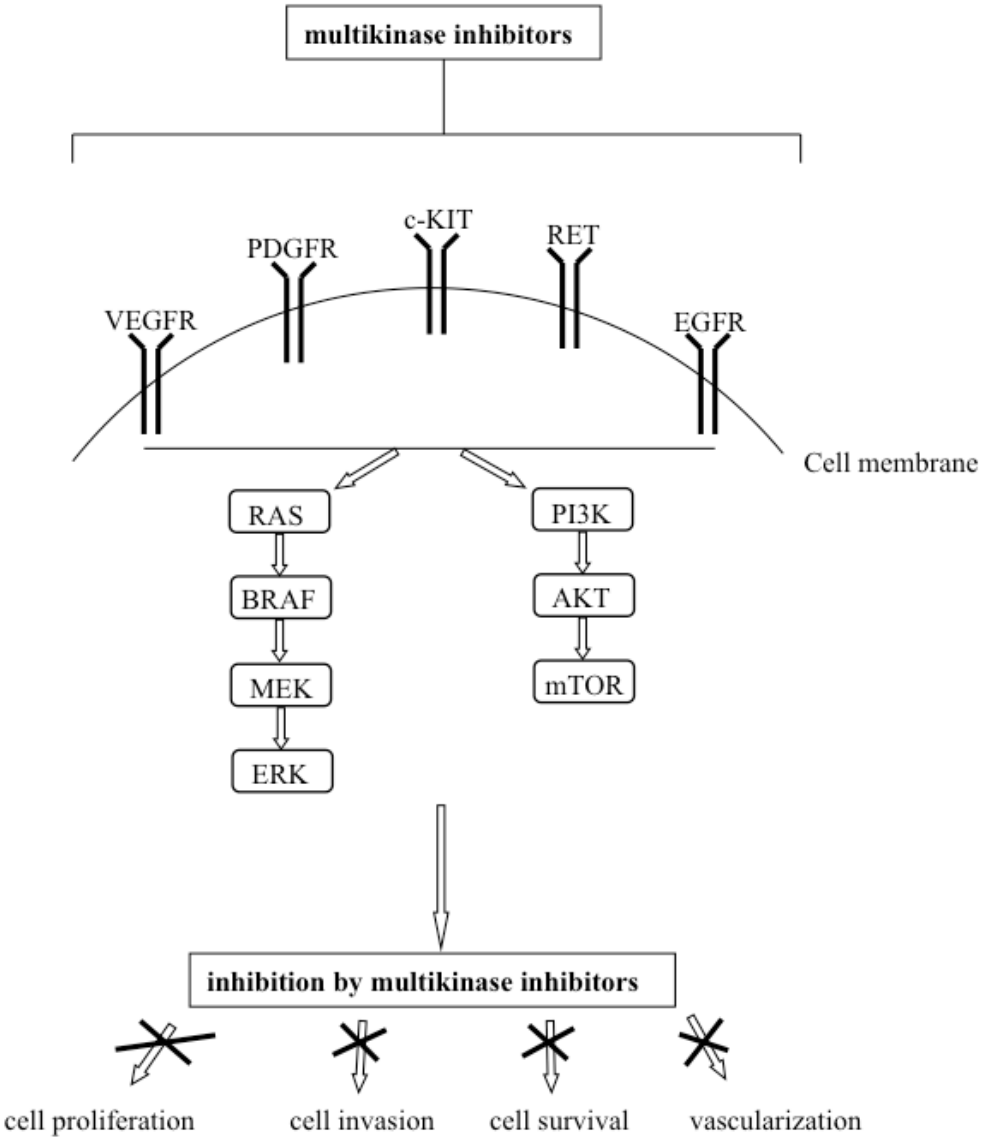
multikinase inhibitors
c-KIT
PDGFR
RET
VEGFR
EGFR
Cell membrane
RAS
PI3K
BRAF
AKT
MEK
mTOR
ERK
inhibition by multikinase inhibitors
cell proliferation
cell invasion
cell survival
vascularization

Figure 1.

Table 1. Multikinase inhibitors and induced hypothyroidism.

Drugs	Main outcomes	References (number)
Sunitinib	Incidence analysis was conducted in 6678 patients administered with sunitinib from 24 eligible trials. All-grade hypothyroidism had an incidence of 9.8% (95% CI 7.3-12.4%), and high-grade of 0.4% (95% CI 0.3-0.5%)	(31)
Sunitinib, cediranib and axitinib	A meta-analysis evaluated 12 clinical trials (6 with sunitinib, 4 with cediranib and 2 with axitinib), after the exclusion of ineligible studies. A higher risk of all-grade hypothyroidism was shown	(33)
Sorafenib	Fifty-seven consecutive patients with HCC, treated with sorafenib, were evaluated. Thyroiditis was developed by 7%. Among the other patients, 30% had elevation of TSH or FT4 above the normal range, and serum T3/reverse T3 ratio and the (T3/T4) ×100 ratio decreased	(35)
Sunitinib	The final results from a global, expanded-access trial in 4543 patients with mRCC, administered with oral sunitinib (50 mg per day on a 4-weeks-on-2-weeks-off schedule), reported all-grade hypothyroidism in 11% of patients	(38)
Sunitinib	A prospective study investigated sunitinib in Japanese patients with mRCC, with an initial oral dose of 50 mg/day on a 4-weeks-on and 2-weeks-off schedule. Hypothyroidism occurred in 35.5%	(39)
Sunitinib	This study investigated the effect of sunitinib in 58 non-screened patients with mRCC. Hypothyroidism occurred in 43% of them	(40)
Sunitinib or sorafenib	A meta-analysis of 500 patients with mRCC in 11 retrospective and prospective studies, treated with sunitinib or sorafenib, did not report a significant difference in PFS between patients who developed hypothyroidism during sunitinib and those who did not	(41)
Lenvatinib or sorafenib	An open-label, phase III, multicentre, trial is conducted in patients with unresectable receiving sorafenib or lenvatinib. Hypothyroidism of any grade was present in 16% of patients receiving lenvatinib and 2% in those receiving sorafenib	(42)
Vandetanib	Thirteen patients with MEN 2B and MTC were evaluated. Among them, 11 had been previously thyroidectomized, and all were administered with vandetanib for more than 6 months. The 11 athyreotic patients had significantly raised TSH levels, while FT4 remained into the normal range, and the levothyroxine dose was increased. In the 2 patients not previously thyroidectomized, FT4 and TSH remained normal in the follow-up	(44)
Cabozantinib	The effect of cabozantinib (60 mg once a day in 28 days cycles) has been evaluated in 17 patients with advanced nonclear cell RCC. The frequency of induced hypothyroidism was 24%	(45)
Cabozantinib	A prospective, phase II trial enrolled patients with platinum-failure, recurrent/metastatic MCC who received oral cabozantinib (60 mg daily until disease progression). Hypothyroidism occurred in 50%	(46)
Sunitinib versus	The randomised phase II CABOSUN trial compared sunitinib with cabozantinib in patients with advanced RCC. Eighteen/78 (23%)	(47)

Adverse event (AE); free	cabozantinib	patients receiving cabozantinib developed hypothyroidism, and 4/72 (6%) treated with sunitinib	
	Lenvatinib	A study evaluated 59 patients with unresectable progressive MTC administered with lenvatinib (24-mg daily, 28-day cycles) until unmanageable toxicity, disease progression, withdrawal, or death. An increase in blood TSH levels occurred in 20%	(48)
	Lenvatinib	A clinical trial is conducted in patients with histologically/clinically confirmed advanced HCC, not submitted to surgical resection or local treatments, and administered with lenvatinib (12 mg once daily in 28-day cycles). Hypothyroidism was present in 21.7%	(49)
	Lenvatinib	A retrospective study investigated lenvatinib (24 mg once daily) in 5 patients with ATC, and 80% showed hypothyroidism of any grade	(50)
	Dasatinib, nilotinib, imatinib, cabozantinib, VEGFR-TKI, axitinib, sorafenib, sunitinib	A review evaluated the AEs of targeted therapy on thyroid function in oncological patients (in 22 original studies and 1641 patients). Hypothyroidism occurred in 33.2%	(51)

thyroxine (FT4); hepatocellular carcinoma (HCC); medullary thyroid cancer (MTC); Merkel cell carcinoma (MCC); metastatic renal cell carcinoma (mRCC); multiple endocrine neoplasia type 2B (MEN 2B); thyroid-stimulating hormone (TSH); triiodothyronine (T3).

Table 2. Multikinase inhibitors and induced hyperthyroidism.

Drugs	Main outcomes	References (number)
Dasatinib, nilotinib, imatinib, cabozantinib, VEGFR-TKI, axitinib, sorafenib, sunitinib	A review evaluated the AEs of targeted therapy on thyroid function in oncological patients (in 22 original studies and 1641 patients). Hyperthyroidism occurred in 3.14%	(51)
Sorafenib, imatinib	A 57-year-old man with lumbar chordoma received 800 mg sorafenib daily. Upon 18 weeks of therapy, the patient developed hyperthyroidism with positive TRAb, even if pre-treatment TSH was normal. Moreover, GD recurred during treatment with imatinib	(52)
Sunitinib	A study investigated the incidence and clinical course of thyrotoxicosis in 62 patients with metastatic mRCC treated with sunitinib. Thyrotoxicosis preceded hypothyroidism in 3.2%	(53)
Cabozantinib	A study evaluated thyroid function in patients enrolled in two phase II clinical trials. Thirty-three patients received cabozantinib for metastatic bladder cancer and metastatic soft tissue sarcoma. Two patients had a transient thyrotoxicosis, and then hypothyroidism	(54)

Adverse event (AE); Graves' disease (GD); metastatic renal cell carcinoma (mRCC).