Thyroid dysfunction and tyrosine kinase inhibitors in renal cell carcinoma

Loredana Bianchi, Luigi Rossi, Federica Tomao¹, Anselmo Papa, Federica Zoratto and Silverio Tomao

Oncology Unit - ICOT, Department of Medico-Surgical Sciences and Biotechnologies, University of Rome 'Sapienza', Latina, Italy

¹Department of Gynecology and Urology, University of Rome 'Sapienza', Rome, Italy

Correspondence
should be addressed
to A Papa
Email
anselmo.papa@libero.it

Abstract

The most recent World Health Organization classification of renal neoplasms encompassed nearly 50 distinctive renal neoplasms. Different histological subtypes have different clinical outcomes and show different responses to therapy. Overall, the incidence of kidney cancer has increased worldwide in the last years. Although the most common type of kidney cancer is localized renal cell carcinoma (RCC), with a 5-year survival rate of 85%, about one third of patients present advanced or metastatic disease at diagnosis, with a 5-year survival rate of only 10%. Multi-targeted receptor tyrosine kinase inhibitors (TKIs, sunitinib and sorafenib), the anti-VEGF MAB bevacizumab in association with interferon- α , and the mTOR inhibitors are now approved for the treatment of mRCC. Recently, the novel agents pazopanib and axitinib have also demonstrated efficacy in mRCC patients. Several recent retrospective and prospective trials have suggested that some of their adverse events, such as hypertension, hypothyroidism, and hand foot syndrome (HFS) may act as potential biomarkers of response and efficacy of treatment. In this review, we analyzed the studies that have suggested a relationship between hypothyroidism onset and a better outcome of mRCC patients treated with TKIs. The biological mechanisms suggesting and explaining this correlation are not well known and different speculative theories have been considered in order to investigate the clinical link between hypothyroidism occurrence and the prolonged therapy with TKIs in solid tumors. Furthermore, the management of this unexplained side effect is very important to maximize the efficacy of therapy in mRCC patients because there is a clear and consistent relationship between drug dose and efficacy of treatment. Certainly, other studies are needed to clarify whether a better outcome is associated with hypothyroidism induced to TKIs in patients with mRCC.

Key Words

- metastatic renal cell carcinoma
- tyrosine kinase inhibitors
- VEGF
- hypothyroidism

Endocrine-Related Cancer
(2013) 20, R233–R245

Introduction

The incidence of kidney cancer has been increasing worldwide, accounting for ~2–3% of all cancers, with a median age at diagnosis of 65 years (Mathew *et al.* 2002, American Cancer Society 2012). The most recent World Health

Organization classification of renal neoplasms encompassed nearly 50 distinctive renal neoplasms. Different histological subtypes have different clinical outcomes and show different responses to therapy (Lopez-Beltran *et al.* 2009).

In Europe, renal cell carcinoma (RCC) is diagnosed in around 88 400 patients each year with 39.300 deaths annually (Ferlay *et al.* 2010). Although the most common type of kidney cancer is localized RCC, with a 5-year survival rate of 85%, about one third of patients present with advanced or metastatic disease (mRCC) at diagnosis (Rabinovitch *et al.* 1994). For these patients, a 5-year survival rate of only 10% was reported (Ries *et al.* 2008).

Several biological investigations on the mechanisms involved in the pathogenesis of advanced RCC have identified new clinically relevant targets of therapy (Ellis & Hicklin 2008, Rini 2009).

Multi-targeted receptor tyrosine kinase inhibitors (TKIs) (sunitinib and sorafenib), the anti-VEGF MAB bevacizumab (in association with interferon- α), and the mTOR inhibitors everolimus and temsirolimus are now approved for the treatment of mRCC (Escudier *et al.* 2007a,b, Hudes *et al.* 2007, Motzer *et al.* 2007, Rini *et al.* 2008). Recently, the novel agents pazopanib and axitinib have also demonstrated efficacy in mRCC patients (Motzer *et al.* 2008, Rini *et al.* 2011). Instead of cytokines, targeted agents are associated with longer median progression-free survival (PFS) of 5–11 months and median overall survival (OS) of 19–26 months (Table 1; Escudier *et al.* 2007, Motzer *et al.* 2007, Rini *et al.* 2008).

TKIs are enzymatic receptor proteins designed to block the ATP-binding site in tyrosine kinases involved in cell proliferation, metastasis, or angiogenesis and, consequently, inhibit signal transduction. Although their mechanism of action is the same, they differ from each other in the spectrum of targeted kinases, pharmacokinetics, and specific adverse events (AEs; Table 2; Hartmann *et al.* 2009).

Sunitinib is an oral inhibitor of different tyrosine kinases, such as VEGFR and platelet-derived growth factor receptor (PDGFR), the stem cell factor KIT receptor, the fms-like tyrosine kinase 3 (FLT3) receptor, and the protein product of the RET oncogene (Abrams *et al.* 2003, Mendel *et al.* 2003, O'Farrell *et al.* 2003, Wilhelm *et al.* 2004, Faivre

et al. 2007, Sulkes 2010, Aparicio-Gallego *et al.* 2011). Sunitinib is approved for the first-line treatment of mRCC (Table 1; Demetri *et al.* 2006, Motzer *et al.* 2006, Goodman *et al.* 2007, Mannavola *et al.* 2007, Wolter *et al.* 2008, Ljungberg *et al.* 2010, Di Lorenzo *et al.* 2011, Fratto *et al.* 2011, Castellano *et al.* 2013).

Sorafenib is a multi-targeted TKI that interacts with VEGFRs, PDGFRB, KIT, RET, BRAF, and RAF1 (Wilhelm *et al.* 2004, Le Tourneau *et al.* 2008, Illouz *et al.* 2009). Sorafenib was the first target agent approved for the treatment of advanced RCC (Table 1; Ratain *et al.* 2006).

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit (Hurwitz *et al.* 2005, Hutson *et al.* 2008a,b, Tamaskar *et al.* 2008). Recently, in a non-inferiority randomized phase III trial, pazopanib was compared with sunitinib in the first-line treatment of patients with mRCC (Table 1; Motzer *et al.* 2012).

The newer agent, axitinib, is a potent, selective, second-generation inhibitor of VEGFR-1, 2, and 3 (Rixe *et al.* 2007, Cohen *et al.* 2008, Rini *et al.* 2009, Schiller *et al.* 2009, Torino *et al.* 2009, La Plant & Louzon 2010, Rugo *et al.* 2011). A recent pivotal phase III trial randomized a total of 723 patients with advanced RCC in order to compare axitinib and sorafenib as second-line therapy (Table 1; Rini *et al.* 2011). Fatigue is an unfavorable side effect occurring during TKI treatment and some authors have shown that it might be at least partially induced by hypothyroidism.

Several recent retrospective and prospective trials have suggested that some of these side effects, such as hypertension, hypothyroidism, and HFS, may serve as potential biomarkers of response and efficacy of treatment. In particular, some studies have suggested a consistent relationship between hypothyroidism and a better outcome of TKI-treated patients with mRCC.

TKI's toxicities

Targeted agents present a pattern of toxicities differing from the common safety profiles occurring with the

Table 1 Overview of efficacy of TKI for mRCC in phase III trials

Study	Drugs	PTS	ORR (%)	P	PFS (months)	P	OS (months)	P
Motzer <i>et al.</i> (2009)	Sunitinib vs INF α	750	47 vs 12	<0.001	11 vs 5	<0.001	26.4 vs 21.8	0.05
Escudier <i>et al.</i> (2007a)	Sorafenib vs placebo	903	NA	NA	5.5 vs 2.8	<0.001	NSS	NSS
Escudier <i>et al.</i> (2009)	Sorafenib vs placebo	903	NA	NA	5.5 vs 2.8	<0.001	17.8 vs 14.3	0.03
Sternberg <i>et al.</i> (2010)	Pazopanib vs placebo	435	30 vs 3	<0.001	9.2 vs 4.2	<0.0001	NA	NA
Motzer <i>et al.</i> (2012)	Pazopanib vs sunitinib	1110	31 vs 25	0.03	10.5 vs 10.2	NA	28.4 vs 29.3	0.28
Rini <i>et al.</i> (2011)	Axitinib vs sorafenib	723	19 vs 9	0.0001	6.7 vs 4.7	<0.0001	NA	NA

PTS, patients; NSS, not statistically significant; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; NA, not available.

Table 2 Toxicities reported in phase III trials conducted on TKI

	Sunitinib (Motzer et al. 2007, 2009) (375 pts)		Sorafenib (Escudier et al. 2007a, 2009) (452 pts)		Pazopanib (Motzer et al. 2012) (554 pts)		Axitinib (Rini et al. 2011) (361 pts)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Cardiovascular toxicity								
Hypertension	30	12	17	4	46	15/<1	40	16
Decline in LVF	13	3	–	–	–	–	–	–
Bleeding	–	–	15	3	–	–	–	–
Thrombosis/embolism	–	–	–	–	–	–	–	–
Respiratory toxicity								
Dyspnea	10	2	14	4	–	–	–	–
Constitutional symptoms								
Fatigue	54	11	29	3	55	10/<1	39	11
Endocrine toxicity								
Hypothyroidism	14	2	–	–	12	–	19	<1
Hyperglycemia	–	–	–	–	54	5/0	–	–
Laboratory								
Hypophosphatemia	31	6	–	13	36	4/0	13	2
Hyperlipasaemia	56	15	41	12	–	–	27	5
Hyperamylasemia	35	5	–	–	–	–	–	–
Bone marrow toxicity								
Lymphopenia	68	16	–	13	38	5/0	33	3
Neutropenia	77	16	–	–	37	4/<1	6	1
Thrombocytopenia	68	8	–	–	41	3/<1	15	<1
Anemia/decreased HB	79	6	8	3	31	1/<1	35	<1
GI and hepatic toxicities								
Anorexia	34	2	14	<1	37	1/0	34	5
Nausea	52	5	19	<1	45	2/0	32	3
Vomiting	31	4	12	1	–	–	24	3
Diarrhea	61	9	48	3	63	9/0	55	11
Hyperbilirubinemia	20	1	–	–	36	3/<1	–	–
↑ AST	56	2	–	–	61	11/1	–	–
↑ ALT	51	2	–	–	60	15/2	–	–
Renal toxicity								
Proteinuria	–	–	–	–	–	–	–	–
Hypercreatininemia	70	<1	–	–	32	<1/0	–	–
Dermatological toxicity								
Rash	24	1	41	1	–	–	13	<1
Hand–foot syndrome	29	9	33	6	29	6/0	27	5
Mucositis/stomatitis	26	2	5	0	–	–	15	1

Pts, patients; GI, gastrointestinal.

conventional chemotherapeutic agents (Di Lorenzo et al. 2011). These side effects are rarely life threatening but can lead to decreased quality of life (Torino et al. 2009).

Many of the most common adverse effects occur during the treatment with all the targeted agents, while others are more specific to one class of agent or to individual agents (Eisen et al. 2012). Commonly reported toxicities of antiangiogenic agents, in patients with mRCC, include typical class effects as fatigue, asthenia, diarrhea, nausea, anorexia, rash, hand–foot skin reaction, and hypertension (Table 2; Demetri et al. 2006, Escudier et al. 2007a, Llovet et al. 2008, Rini et al. 2010, 2011, Di Lorenzo et al. 2011, Fratto et al. 2011).

Several recent retrospective and prospective trials have suggested that some of these side effects, such as hypertension, hypothyroidism, and HFS, may serve as potential biomarkers of response and efficacy of treatment. In particular, a lot of studies have suggested the relationship between hypothyroidism and a better outcome in TKI-treated patients with mRCC.

Thyroid and hypothyroidism

Thyroid hormones play an important role in the development and function of multiple organs. Thyroid hormone exists in two forms, 3,3',5,5'-tetraiodothyronine (T₄) and

3,3',5-triiodothyronine (T₃), both produced and secreted by the follicular cells of the thyroid gland (Schwartz & Stevenson 2007). The action of thyroid hormone is mediated through the binding of T₃ to nuclear thyroid hormone receptors, which function as transcription factors (Oberg *et al.* 2001), within the target cell. The intracellular concentrations of T₃ are modulated by deiodinating enzyme: in particular, the type 2 deiodinase (D2) converts the precursor T₄ to T₃, whereas D3 degrades T₄ to rT₃ and T₃ to 3,3-diiodothyronine (T₂), two inactive forms (Gereben *et al.* 2008).

The prevalence of hypothyroidism in the general population ranges from 3.8 to 4.6% (Tunbridge *et al.* 1977, Vanderpump *et al.* 1995, Hollowell *et al.* 2002, Leese *et al.* 2008). Hypothyroidism has different etiologies and manifestations and may be subclinical or overt. Subclinical hypothyroidism is defined as a serum TSH above the upper reference limit in combination with a normal free T₄ level. An elevated TSH, usually above 10 mIU/l and associated with a subnormal free T₄, characterizes overt hypothyroiditis (Garber *et al.* 2012).

In iodine sufficiency areas, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's thyroiditis) (Garber *et al.* 2012). However, in many countries, iodine deficiency is still an important cause of hypothyroidism (Andersson *et al.* 2007). Transient hypothyroidism may occur in subacute (de Quervain's) thyroiditis and in *post partum* thyroiditis (Roberts & Ladenson 2004), while congenital hypothyroidism, due to thyroid gland agenesis or dyshormonogenesis, affects about one in 4000 newborns (Roberts & Ladenson 2004). Other

common causes of hypothyroidism include thyroidectomy, radioiodine therapy, and drugs such as amiodarone, lithium, interferon, sunitinib, and rifampicin (Chakera *et al.* 2012).

Moreover, insufficient production of bioactive TSH causes central hypothyroidism (Utiger 1965, Beck-Peccoz *et al.* 1985) due to pituitary or hypothalamic disorders such as tumors, hemorrhagic necrosis (Sheehan's syndrome), inflammatory or infiltrative diseases, or surgical and radiation treatment. The most common clinical features associated with hypothyroidism are fatigue, dry skin, cold intolerance, muscle weakness, and constipation (Garber *et al.* 2012).

TKI-induced hypothyroidism

Target agents are known to affect thyroid homeostasis, but the precise mechanisms are not well understood. Severe hypothyroidism associated with use of these agents in mRCC is infrequent and typically can be corrected by use of thyroid hormone replacement therapy (Fujiwara *et al.* 2012). Biochemical and clinical hypothyroidism is commonly reported in patients with mRCC receiving sunitinib and sorafenib (Table 3; Rini *et al.* 2007, Tamaskar *et al.* 2008, Miyake *et al.* 2010).

Sunitinib

Thyroid dysfunction is a well-known adverse effect of sunitinib (Illouz *et al.* 2009, Torino *et al.* 2009) and occurred in 14% of mRCC patients enrolled in the phase 3 trial, including 2% with grade 3 and 4 severity (Motzer *et al.* 2009,

Table 3 Incidence of hypothyroidism in clinical studies with TKI for mRCC

Study	TKI	PTS (n)	HT (%)	G3–G4 (%)	Predictive remarks of outcome
Rini <i>et al.</i> (2007)	Sunitinib	66	85	NA	NR
Wolter <i>et al.</i> (2008)	Sunitinib	59	61	NA	NR
Motzer <i>et al.</i> (2009)	Sunitinib	750	14	2	NR
Shinohara <i>et al.</i> (2011)	Sunitinib	17	53	NA	NR
Riesenbeck <i>et al.</i> (2011)	Sunitinib/sorafenib	66	32	NA	Yes
Schmidinger <i>et al.</i> (2011)	Sunitinib/sorafenib	83	36	NA	Yes
Baldazzi <i>et al.</i> (2012)	Sunitinib	22	59	NA	Yes
Sabatier <i>et al.</i> (2012)	Sunitinib	102	50	NA	No
Tamaskar <i>et al.</i> (2008)	Sorafenib	39	18	NA	NR
Miyake <i>et al.</i> (2010)	Sorafenib	69	68	NA	NR
Rini <i>et al.</i> (2011)	Sorafenib	355	8	<1	NR
Sternberg <i>et al.</i> (2010)	Pazopanib	290	<10	<1	NR
Motzer <i>et al.</i> (2012)	Pazopanib	557	12	NA	NR
Rini <i>et al.</i> (2011)	Axitinib	359	19	<1	NR
Tomita <i>et al.</i> (2011)	Axitinib	64	31	NA	NR

PTS, patients; HT, hypothyroidism; NR, not reported; NA, not available.

Di Lorenzo *et al.* 2011). Instead, hypothyroidism was reported in 2% of patients treated with IFN- α (Motzer *et al.* 2009).

Retrospective studies have indicated that sunitinib can induce hypothyroidism, including subclinical hypothyroidism, in 53–85% of patients (Rini *et al.* 2007, Wong *et al.* 2007). In prospective and observational studies, this complication has been reported in 53–85% of patients (Table 3; Desai *et al.* 2006, Mannavola *et al.* 2007, Wolter *et al.* 2008, Riesenbeck *et al.* 2011, Schmidinger *et al.* 2011, Shinohara *et al.* 2011, Baldazzi *et al.* 2012, Sabatier *et al.* 2012).

There is a discrepancy between incidence rates reported in prospective and retrospective trials, most likely due to lack of frequent monitoring of thyroid function, particularly in early studies, before hypothyroidism was recognized as a common side effect of target therapy (Kollmannsberger *et al.* 2011).

A possible relationship between sunitinib and hypothyroidism was first noted since 2005 (Schöffski *et al.* 2006a, Wolter *et al.* 2007), when sporadic cases of thyroid dysfunction were identified during sunitinib treatment (Table 3). On this evidence, the phenomenon was evaluated in small retrospective and prospective studies (Schöffski *et al.* 2006b), and an unexpected high incidence of hypothyroidism in both groups of patients occurred (57 and 37% respectively). This toxicity was not previously included among sunitinib side effects (Motzer *et al.* 2007). Since these observations, other groups have also successively described the relationship between sunitinib and hypothyroidism (Makita & Iiri 2013), although the previous studies were limited by factors related to study design, including variable definition of hypothyroidism, and bias about evaluation of thyroid function (Table 3; Wolter *et al.* 2008).

In the study of Desai *et al.* (2006), 62% of 42 patients with imatinib-resistant GIST showed alterations in TSH levels under sunitinib, and risk increased with treatment duration. Thyroid dysfunction was also observed in 85% of 66 patients with sunitinib-treated mRCC in Rini *et al.* (Table 3) and in 60% of RCC or GIST patients involved in a prospective study about sunitinib-induced hypothyroidism by Wolter (Vetter *et al.* 2008).

Sunitinib-related hypothyroidism occurs, on average, from 12 to 50 weeks after starting of treatment (Vetter *et al.* 2008), and it is generally identified after two cycles of therapy (Motzer *et al.* 2007). Longer duration of sunitinib administration correlates with increased chance of onset of thyroid dysfunction (Vetter *et al.* 2008). Usually, hypothyroidism becomes worse over time; rarely, severe hypothyroidism suddenly develops (Mannavola *et al.*

2007). In fact, sunitinib-induced thyroid dysfunction can present as TSH elevation only, with normal T₄ levels (subclinical hypothyroidism) or TSH elevation and low T₄ (overt hypothyroidism), that is more frequently associated with clinical features of hypothyroidism (Kollmannsberger *et al.* 2011). About 84% of patients with sunitinib-induced hypothyroidism show clinical symptoms (Motzer *et al.* 2007) and about 50% require thyroid hormone substitution therapy, with an improvement of symptoms in 50% of patients (Wong *et al.* 2007, Illouz *et al.* 2009).

According to different studies, sunitinib-related hypothyroidism is initially transient, showing with altered TSH levels during ON periods of treatments only, and becomes a lasting dysfunction after many cycles of treatment (Mannavola *et al.* 2007, Illouz *et al.* 2009).

Sorafenib and pazopanib

Sorafenib-induced hypothyroidism does not occur as frequently as sunitinib-induced hypothyroidism (Table 3; Tamaskar *et al.* 2008, Schmidinger *et al.* 2011). Patients treated with sunitinib have a twofold increased risk of requiring thyroid hormone replacement therapy compared with sorafenib. Hypothyroidism was not listed as a common AE in phase III studies of sorafenib or pazopanib (Escudier *et al.* 2007a, 2009, Sternberg *et al.* 2010); however, a randomized, double-blinded, placebo-controlled phase III study (La Plant & Louzon 2010) identified thyroid dysfunction attributable to pazopanib with an incidence of fewer than 10% ($\leq 7\%$) in patients treated for mRCC, with grade 3/4 events reported in $<1\%$ of patients (Sternberg *et al.* 2010). These results have been confirmed by another randomized, open-label, phase III trial of pazopanib vs sunitinib (Motzer *et al.* 2012) where hypothyroidism occurred among 12% of patients treated with pazopanib (Table 3; Motzer *et al.* 2012).

A retrospective study of 39 patients treated with sorafenib (Tamaskar *et al.* 2008) identified thyroid dysfunction attributable to the drug in 21% of patients; moreover, a prospective study in a cohort of Japanese patients (Miyake *et al.* 2010) suggested that hypothyroidism may occur more frequently in Japanese than in Western patients. Sorafenib-induced hypothyroidism can persist after withdrawal of treatment (Illouz *et al.* 2009).

Axitinib

In a phase III study comparing axitinib with sorafenib (Rini *et al.* 2011), hypothyroidism occurred more frequently with axitinib than with sorafenib (19 and 8%

respectively) (Table 3). In two phase I trials, conducted on 18 Japanese patients, evaluating the safety, pharmacokinetic, and antitumor activity of axitinib, 16 patients (89%) experienced TSH elevation. So increased TSH levels were highly correlated with exposure to axitinib. Moreover, in six patients, thyroid hormone replacement therapy showed an improvement on the onset of axitinib-related grade 3/4 fatigue. Another study of 16 patients with mRCC, treated with sunitinib, sorafenib, or axitinib for more than 12 months, showed that thyroid dysfunction was a common toxicity occurring in ~40% of patients (Vakkalanka *et al.* 2008).

Mechanism of TKI-induced hypothyroidism

The molecular mechanisms of sunitinib-induced hypothyroidism are currently unknown (Wolter *et al.* 2008). Different mechanisms have been considered in order to explain the onset of this hypothyroidism.

VEGF inhibition

Sunitinib may have a direct effect on the thyroid gland, for example, through the inhibition of VEGFR and/or PDGFR. Recent studies on mouse models have shown that VEGFR inhibition can cause capillary regression in different organs and that vasculature of the thyroid has the greatest regression of all organs (Baffert *et al.* 2006, Kamba *et al.* 2006) because thyroid gland is well vascularized and shows the highest blood flow rates per unit weight of any tissue in the body (Wang *et al.* 1998). Interestingly, in this animal model, thyroid capillaries regenerated in the absence of VEGFR inhibition. This phenomenon may explain the rhythmic pattern of TSH observed in patients treated with sunitinib.

Another *in vivo* study supports this hypothesis: rats exposed to sunitinib for 8 days showed a decrease in thyroid microvessels and vessel-to-follicle ratio on histological examination and recovered after sunitinib withdrawal (Kappers *et al.* 2011). Maybe, when ischemia becomes too severe for thyrocytes to survive, apoptosis brings to destructive thyroiditis without autoimmune disorders (Makita *et al.* 2010).

Moreover, a metabolic hypothesis, in addition to a capillary regression hypothesis for explaining sunitinib-induced hypothyroidism (Kappers *et al.* 2011). Authors showed that in sunitinib-treated rats, serum T₄ and T₃ decreased with an increase in TSH levels. They also interestingly reported increased D3 activity that degrades T₄ to rT₃ and T₃ to T₂, two inactive forms (Gereben *et al.* 2008), and decreased D1 activity that activates thyroid

hormone by converting the pro-hormone T₄ by outer ring deiodination to bioactive T₃ with a consequent TSH increase, in rats with histologically marked capillary regression (Kappers *et al.* 2011). Previous study (Simonides *et al.* 2008) showed that hypoxia induces expression of the D3 gene via a hypoxia-inducible factor (HIF)-dependent pathway. So sunitinib may induce hypoxia, and consequently, HIF-1 expression, through its antiangiogenic effects, with increased expression of *Dio3* gene in peripheral tissues.

Radioiodine thyroidal uptake

A recent study suggests a sunitinib-induced inhibition in radioiodine thyroidal uptake (Mannavola *et al.* 2007). Radioiodine uptake impairment has been suggested by the observation of a reduced uptake on scintiscan at the end of ON periods with a partial or total recovery at the end of OFF period. Thyroid dysfunction, as well as inhibition of iodine uptake, is transient, showing only during treatment. In fact, within 2 months after sunitinib withdrawal, alterations in TSH levels disappear (Mannavola *et al.* 2007). A competitive inhibition of iodine on sodium iodine symporter by fluorine, contained in high doses in sunitinib, can be hypothesized as the underlying mechanism. Nonetheless, normal fluorine levels found in treated patients seem not to confirm this hypothesis (Zygulska *et al.* 2012). Instead, the hypothesis of iodine uptake blockage has been rejected by a study on rat thyroid cells (Salem *et al.* 2008).

TPO inhibition

Sunitinib may also inhibit TPO activity leading to reduced synthesis of the thyroid hormones, as suggested by *in vitro* studies (Wong *et al.* 2007).

Autoimmunological process

A presumable autoimmunological damage on thyroid gland by sunitinib comes from the observation of cases of lymphocytic thyroiditis among patients receiving the drug (Alexandrescu *et al.* 2008, Wolter *et al.* 2008), but different studies (Mannavola *et al.* 2007, Rini *et al.* 2007) have excluded autoimmunological background.

Thyroid hormone metabolism

Abdulrahman hypothesized the influence of sorafenib on iodothyronine deiodinase (D1, D2, and D3) activity,

resulting in enhanced T_4 and T_3 metabolism that may contribute to hypothyroidism during sorafenib therapy (Abdulrahman *et al.* 2010).

Impairment of transmembrane transport

TKIs could also hinder transmembrane transport of thyroid hormones that maybe fitting into iodothyronine binding sites of transmembrane transporters (Braun *et al.* 2012).

TSH pathway

RAF pathway is involved in TSH signal transduction cascade and it is a target of sorafenib. So inhibition of this pathway may contribute to sorafenib-related hypothyroidism (Rivas & Santisteban 2003, Calebiro *et al.* 2006). However, no study has analyzed the effect of inhibition of this pathway on thyroid hormone synthesis.

Hypothyroidism and tumor's outcome

The influence of hypothyroidism on cancer survival has been suspected in several studies (Garfield *et al.* 2007). It has been suggested that the thyroid hormone, through stimulation of other growth factors, may represent a growth-stimulating signal in several tumor types (Trentin *et al.* 2001). Thyroid hormones may be permissive for tumor growth and may reduce survival in recurrent brain tumors (Herbergs *et al.* 2003) and in head and neck cancer (Nelson *et al.* 2006). Moreover, a relationship between hypothyroidism and reduced incidence and less aggressiveness of breast cancer was demonstrated (Cristofanilli *et al.* 2005). In 2007, Oetting Alexis demonstrated that thyroid hormones play important roles in proliferation and apoptosis (Oetting 2007).

Verga Falzacappa *et al.* (2009) has demonstrated how the granulosa cell population can be considered a thyroid hormone target, being as how their survival is induced by 3,5,30-triiodothyronine (T_3) under specific circumstances via cell cycle and metabolism regulation, strengthening the consideration of this hormone as a survival factor. In addition, a recent work has evidenced an antiapoptotic action on rat granulosa cells exerted by T_3 together with FSH (Zhang *et al.* 2011). Nonetheless, growing evidence indicates that the thyroid hormones might induce cell survival against various insults, both physiological and pharmacological, in different cellular systems (Verga Falzacappa *et al.* 2006). Recently, Verga Falzacappa *et al.* (2012) demonstrated for the first time that thyroid

hormone T_3 is able to block the cytotoxic effect of taxanes on rGROV granulosa cells, granting the cells to cycle regularly, escaping apoptosis.

In particular, caspase 3 is the most characterized effector caspase required for granulosa cell apoptosis, as follicles from caspase 3-null ovaries do not show granulosa cell apoptosis in response to serum starvation (Matikainen *et al.* 2001).

In their work, the authors demonstrated how the caspase 3 active form is strongly downregulated by T_3 , even when there is a tight activation signal triggered by paclitaxel (Verga Falzacappa *et al.* 2012). Moreover, the ability of T_3 to act as an antiapoptotic factor has been demonstrated in diverse cell systems and different pro- and antiapoptotic factors have been evidenced as targets of T_3 action (Sukocheva & Carpenter 2006).

As just highlighted, within the cell, T_3 is the more potent hormone, and the major pathway for the production of circulating T_3 is via 5' deiodination of the outer ring of T_4 by selenoproteins known as deiodinases (Kohrle 2000). The predominant activity of type III deiodinase described in different tumors and also in kidney cancer due to sunitinib-induced hypoxia may lead to a diminished availability of T_3 and consequently the loss of its antiapoptotic activity (Dentice *et al.* 2009, Kappers *et al.* 2011). A preliminary report on patients treated with sunitinib for mRCC suggested that hypothyroid patients showed significantly longer PFS than euthyroid patients (Wolter *et al.* 2008).

Most recently, a retrospective chart review was performed in patients treated with sunitinib or sorafenib from 2005 to 2011: 44% of patients treated with sunitinib and 27% of patients treated with sorafenib developed hypothyroidism. There was a statistically significant difference in the PFS between hypothyroid patients and euthyroid ones (18.2 vs 10.1 months respectively) (Clemons *et al.* 2012).

Another retrospective analysis showed that hypothyroidism occurred in 52% of patients treated with sunitinib for mRCC, within 3 months of treatment initiation. The hypothyroid patients tended to have longer PFS and longer OS than the euthyroid patients (Sella *et al.* 2012).

A prospective analysis by Schmidinger *et al.* (2011), for the first time, investigated whether the occurrence of hypothyroidism during treatment with sunitinib and sorafenib affects the outcome of patients with mRCC (Schmidinger *et al.* 2011). There was a statistically significant correlation between the occurrence of hypothyroidism during treatment and the rate of objective remission: hypothyroid patients showed higher ORR than euthyroid patients (28.3 vs 3.3% respectively;

$P < 0.001$) and prolonged median OS (not reached vs 13.9 months respectively; $P = 0.016$). In multivariate analysis, the development of subclinical hypothyroidism was identified as an independent predictor of survival (HR = 0.31; $P = 0.014$) (Schmidinger et al. 2011). These results suggested that hypothyroidism improves response to treatment with sunitinib or sorafenib, but it is not enough to define hypothyroidism as a biomarker (Castellano et al. 2013).

Successively, other prospective and observational studies showed improved outcomes in patients developing TKI-related hypothyroidism; in Riesenbeck et al.'s study (Riesenbeck et al. 2011), 31.8% of patients receiving sunitinib or sorafenib became hypothyroid, and hypothyroidism was associated with a longer PFS (16.0 vs 6.0 months, $P = 0.032$) (Riesenbeck et al. 2011). Likewise, in Baldazzi et al. (2012), 59.1% of patients during sunitinib treatment developed thyroid failure, with a median PFS of 8.55 months instead of 7.03 months in euthyroid patients ($P < 0.05$) (Baldazzi et al. 2012).

According to Fujiwara et al. (2012), as changes in TSH levels correlated with axitinib plasma levels, TSH may potentially act as biomarkers of axitinib exposure. However, further clinical investigation is necessary to clarify the clinical usefulness of these potential biomarkers (Fujiwara et al. 2012).

It would seem that hypothyroidism no longer should be perceived as an unwanted side effect of treatment but, rather, as predictive marker of treatment outcome in patients with mRCC (Schmidinger et al. 2011).

Moreover, a meta-analysis of mRCC studies showed that higher exposure to sunitinib is correlated with longer time to progression, longer OS, and higher probability of decrease in tumor size or halting tumor growth (Houk et al. 2010). So this study demonstrated the importance of achieving and maintaining optimal exposure to sunitinib. Despite these described evidences, Sabatier et al. (2012) in a prospective observational multicenter study have shown that abnormal thyroid function did not increase survival among patients with mRCC treated with sunitinib. In fact, among 102 patients with normal baseline thyroid function, 53% developed thyroid dysfunction and median PFS was not different between the groups with abnormal or normal thyroid function after 6 months of treatment (18.9 and 15.9 months respectively).

The authors criticize statistical methods used by Schmidinger et al. (2011) and Wolter in their studies; in Wolter study, early progressive and died patients were interpreted like euthyroid ones; instead, for these patients, an alteration of thyroid function could appear later in

their natural history. Another bias was the lack of definition of a landmark time of onset of hypothyroidism, while for using a prognostic marker, this one must be assessed at a precise and shared time, the so-called diagnosis time.

Schmidinger et al. (2011) showed a statistically significant improvement of OS but not of PFS in hypothyroid patients. It was not specified what therapies were carried out after progression with sunitinib or sorafenib in hypothyroid and euthyroid patients, and how these treatments could have modified OS (Sabatier et al. 2012). Instead, Sabatier et al. (2012) tried to cancel all these bias.

TKI's hypothyroidism and its management

The management of hypothyroidism is important for controlling associated symptoms such as fatigue (Eisen et al. 2012). This one could be either related to disease itself, either a treatment toxicity, above all under sunitinib (11% for grades 3 and 4) (Motzer et al. 2009). Moreover, fatigue may also be a direct hypothyroidism consequence. However, it is important to identify the etiology of TKI-associated asthenia, in particular, if it is related to a curable cause (Sabatier et al. 2012).

According to most authors, any preexisting hypothyroidism should be detected and treated before starting TKI treatment. There is less consensus on the management once treatment with sunitinib is in progress. For example, Wolter et al. (2007) suggest an assessment of thyroid function on days 1 and 28 of the 6-week cycle for the first four cycles of sunitinib treatment because the peak in TSH levels was reported to occur after 4 weeks of treatment with sunitinib (Wolter et al. 2007). If TSH levels remain normal, these authors recommend to reduce the frequency of monitoring to once every three cycles (on day 28), and every fourth cycle if TSH levels are abnormal, without overt hypothyroidism (Wolter et al. 2007).

Subclinical hypothyroidism exerts its detrimental effect in a time longer than the treatment with TKI, and if one assume that hypothyroidism improves the efficacy of some TKIs, then T_4 treatment should be initiated only in the presence of clinical hypothyroidism. In fact, exogenous thyroid hormones should be administered in symptomatic patients with normal free thyroxine (FTI) levels but elevated TSH levels (threshold value: 10 mIU/l) and in patients with overt hypothyroidism (Schwandt et al. 2009). Patients with abnormal thyroid function at baseline (before TKIs initiation), with previous thyroid hormone replacement due to

underlying thyroid disease, were excluded from majority of the studies.

In the report by Desai *et al.* seven (10%) of 69 patients were noted to have an elevated level of TSH before treatment with sunitinib and an additional eight (12%) were being treated with L-thyroxine replacement therapy before enrollment. Thus, 22% of patients had evidence of abnormal thyroid function at baseline (Desai *et al.* 2006).

Most authors agree that any preexisting hypothyroidism should be detected and treated before starting sunitinib treatment, as recommended in the European summary of product characteristics (Eisen *et al.* 2012). Furthermore, patients who are already hypothyroid and are exposed to TKI require monitoring and treatment similar to that of patients not hypothyroid before the initiation of TKI treatment.

Instead, Torino *et al.* (2009) suggest evaluation of thyroid function on day 1 of every cycle of sunitinib treatment because measurement at day 28 of the cycle (at the end of the 4-week sunitinib treatment period) may increase the chances of early detection of hypothyroidism; usually, this dysfunction may be transient and/or subclinical and not require therapy. Screening for hypothyroidism, as recommended in the drug package insert, can be conducted for pazopanib and axitinib in a similar way, with thyroid assessments approximately every 8 weeks (Fig. 1; Di Lorenzo *et al.* 2011).

Discussion

High incidence of thyroid dysfunction has been reported in patients treated with TKI. In particular, hypothyroidism is clearly associated with sunitinib and, even if less frequently, with sorafenib, pazopanib, and axitinib. Sunitinib-related hypothyroidism can be either subclinical or overt and, generally, it is diagnosed after two cycles of treatment, with an increasing risk related to the duration of treatment. Typically, hypothyroidism is initially intermittent and transient, with high levels of TSH at the end of the ON period of treatment and normalization at the end of the OFF period. It becomes permanent after several cycles of treatment. Sorafenib-induced hypothyroidism can persist after conclusion of therapy.

Although the exact molecular mechanisms have not been well clarified, several hypotheses have been proposed to explain thyroid dysfunction related to TKI, such as inhibition of VEGFR and/or PDGFR, leading to thyroid capillary regression, inhibition in radioiodine

thyroidal uptake, autoimmunological process, inhibition of TPO activity, and impairment of thyroid hormone's metabolism.

A lot of studies have shown how TKI-induced hypothyroidism seems to be related to a better outcome of mRCC patients. Perhaps thyroid hormones promote tumor growth through stimulation of growth factors, and, consequently, hypothyroidism could improve efficacy of treatment with TKI. Nonetheless, growing evidence indicates that the thyroid hormones might induce cell survival against various insults, both physiological and pharmacological, in different cellular systems. Moreover, the ability of T₃ to act as an antiapoptotic factor has been demonstrated in diverse cell systems and different pro- and antiapoptotic factors have been evidenced as targets of T₃ action.

According to both retrospective and prospective studies, patients developing thyroid dysfunction during treatment for mRCC show longer PFS, ORR, and OS than patients that remain euthyroid. So these data suggest a possible role of TKI-related hypothyroidism as a biomarker of response to treatment in patients with mRCC. On the other hand, a single prospective observational multicenter analysis disproved this hypothesis criticizing statistical methods used by other authors and requiring more standardized parameters in order to remove bias that compromise results of these studies. Because of the small number of patients involved in this study, larger comparative analyses are thus needed to validate these conclusions. However, strong association between TKI treatment and thyroid impairment imposes close monitoring of thyroid function before and during therapy. In this review, we reported different models of proposed management of TKI-treated patients with mRCC, with recommendation of replacement therapy where needed, in order to avoid clinical symptoms caused by thyroid dysfunction.

The main goal of management is to maximize the efficacy of treatment for mRCC patients, due to the suspected relationship between dosage and efficacy, minimizing the impact of side effects and, thus, the necessity of dose reduction; consequently, if one assumes that hypothyroidism improves the efficacy of some TKIs, then T₄ treatment should be initiated only in symptomatic patients with normal FTI levels but elevated TSH levels and in patients with overt hypothyroidism. Moreover, other studies are needed to clarify the relationship between TKI-induced hypothyroidism and the outcome of patients with mRCC.

Declaration of interest

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

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

- Abdulahman RM, Verloop H, Hoftijzer H, Verburg E, Hovens GC, Corssmit EP, Reiners C, Gelderblom H, Pereira AM, Kapiteijn E *et al.* 2010 Sorafenib-induced hypothyroidism is associated with increased type 3 deiodination. *Journal of Clinical Endocrinology and Metabolism* **95** 3758–3762. (doi:10.1210/jc.2009-2507)
- Abrams TJ, Lee LB, Murray LJ, Prjer NK & Cherrington JM 2003 SU11248 inhibit KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. *Molecular Cancer Therapeutics* **2** 471–478.
- Alexandrescu DT, Popoveniuc G, Farzanmehr H, Dasanu CA, Dawson N & Wartofsky L 2008 Sunitinib associated lymphocytic thyroiditis without circulating antithyroid antibodies. *Thyroid* **18** 809–812. (doi:10.1089/thy.2007.0349)
- American Cancer Society: Cancer Facts and Figures 2012. Atlanta GACS, 2012. Atlanta, GA, USA: American Cancer Society.
- Andersson M, de Benoist B, Delange F & Zupan J 2007 Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutrition* **10** 1606–1611. (doi:10.1017/S1368980007000092)
- Aparicio-Gallego G, Blanco M, Figueroa A, García-Campelo R, Valladares-Ayerbes M, Grande-Pulido E & Antón-Aparicio L 2011 New insight into molecular mechanism of sunitinib-associated side effect. *Molecular Cancer Therapeutics* **10** 2215–2223. (doi:10.1158/1535-7163.MCT-10-1124)
- Baffert F, Le T, Sennino B, Thurston G, Kuo CJ, Hu-Lowe D & McDonald DM 2006 Cellular changes in normal blood capillaries undergoing regression after inhibition of VEGF signaling. *American Journal of Physiology. Heart and Circulatory Physiology* **290** H547–H559. (doi:10.1152/ajpheart.00616.2005)
- Baldazzi V, Tassi R, Lapini A, Santomaggio C, Carini M & Mazzanti R 2012 The impact of sunitinib-induced hypothyroidism on progression-free survival of metastatic renal cancer patients: a prospective single-center study. *Urologic Oncology* **30** 704–710. (doi:10.1016/j.urolonc.2010.07.015)
- Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G & Weintraub BD 1985 Decreased receptor binding of bio-logically inactive thyrotropin in central hypothyroidism. Effect of treatment with thyrotropin-releasing hormone. *New England Journal of Medicine* **312** 1085–1090. (doi:10.1056/NEJM198504253121703)
- Braun D, Kim TD, le Coutre P, Kohrle J, Hershman JM & Schweizer U 2012 Tyrosine kinase inhibitors noncompetitively inhibit MCT8-mediated iodothyronine transport. *Journal of Clinical Endocrinology and Metabolism* **97** E100–E105. (doi:10.1210/jc.2011-1837)
- Calebiro D, de Filippis T, Lucchi S, Martinez F, Porazzi P, Trivellato R, Locati M, Beck-Peccoz P & Persani L 2006 Selective modulation of protein kinase A I and II reveals distinct roles in thyroid cell gene expression and growth. *Molecular Endocrinology* **20** 3196–3211. (doi:10.1210/me.2005-0493)
- Castellano D, Ravaud A, Schmidinger M, De Velasco G & Vazquez F 2013 Therapy management with sunitinib in patients with metastatic renal cell carcinoma: key concepts and the impact of clinical biomarkers. *Cancer Treatment Reviews* **39** 230–240. (doi:10.1016/j.ctrv.2012.04.009)
- Chakera AJ, Pearce SHS & Vaidya B 2012 Treatment for primary hypothyroidism: current approaches and future possibilities. *Drug Design, Development and Therapy* **6** 1–11.
- Clemons J, Gao D, Naam M, Breaker K, Garfield D & Flaig TW 2012 Thyroid dysfunction in patients treated with sunitinib or sorafenib. *Clinical Genitourinary Cancer* **10** 225–231. (doi:10.1016/j.clgc.2012.08.002)
- Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, Kane MA, Sherman E, Kim S, Bycott P *et al.* 2008 Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *Journal of Clinical Oncology* **26** 4708–4713. (doi:10.1200/JCO.2007.15.9566)
- Cristofanilli M, Yamamura Y, Kau SW, Bevers T, Strom S, Patangan M, Hsu L, Krishnamurthy S, Theriault RL & Hortobagyi GN 2005 Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. *Cancer* **103** 1122–1128. (doi:10.1002/cncr.20881)
- Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA *et al.* 2006 Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* **368** 1329–1338. (doi:10.1016/S0140-6736(06)69446-4)
- Dentice M, Ambrosio R & Salvatore D 2009 Role of type 3 deiodinase in cancer. *Expert Opinion on Therapeutic Targets* **13** 1363–1373. (doi:10.1517/14728220903339122)
- Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH, Morgan JA, Dychter SS, Larsen PR, Demetri GD *et al.* 2006 Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Annals of Internal Medicine* **145** 660–664. (doi:10.7326/0003-4819-145-9-200611070-00008)
- Di Lorenzo G, Porta C, Bellmunt J, Sternberg C, Kirkali Z, Staehler M, Joniau S, Montorsi F & Buonerba C 2011 Toxicities of targeted therapy and their management in kidney cancer. *European Urology* **59** 526–540. (doi:10.1016/j.eururo.2011.01.002)
- Eisen T, Sternberg CN, Robert C, Mulders P, Pyle L, Zbinden S, Izzedine H & Escudier B 2012 Targeted therapies for renal cell carcinoma: review of adverse event management strategies. *Journal of the National Cancer Institute* **104** 93–113. (doi:10.1093/jnci/djr511)
- Ellis LM & Hicklin DJ 2008 VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nature Reviews. Cancer* **8** 579–591. (doi:10.1038/nrc2403)
- Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA *et al.* 2007a Sorafenib in advanced clear-cell renal carcinoma. *New England Journal of Medicine* **356** 125–134. (doi:10.1056/NEJMoa060655)
- Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, Chevreau C, Fiipek M, Melichar B & Bajetta E 2007b Bevacizumab plus interferon α -2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* **370** 2103–2111. (doi:10.1016/S0140-6736(07)61904-7)
- Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, Negrier S, Chevreau C, Desai AA, Rolland F *et al.* 2009 Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *Journal of Clinical Oncology* **27** 3312–3318. (doi:10.1200/JCO.2008.19.5511)
- Faivre S, Demetri G, Sargent W & Raymond E 2007 Molecular basis for sunitinib efficacy and future clinical development. *Nature Reviews. Drug Discovery* **6** 734–745. (doi:10.1038/nrd2380)
- Ferlay J, Parkin DM & Steliarova-Foucher E 2010 Estimates of cancer incidence and mortality in Europe in 2008. *European Journal of Cancer* **46** 765–781. (doi:10.1016/j.ejca.2009.12.014)
- Fratto ME, Imperatori M, Vincenzi B, Tomao F, Santini D & Tonini G 2011 New perspectives: role of sunitinib in breast cancer. *La Clinica Terapeutica* **162** 251–257.

- Fujiwara Y, Kiyota N, Chayahara N, Suzuki A, Umeyama Y, Mukohara T & Minami H 2012 Management of axitinib (AG-013736)-induced fatigue and thyroid dysfunction, and predictive biomarkers of axitinib exposure: results from phase I studies in Japanese patients. *Investigational New Drugs* **30** 1055–1064. (doi:10.1007/s10637-011-9637-1)
- Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JL, Pessah-Pollack R, Singer PA & Woeber KA 2012 Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocrine Practice* **18** 988–1028.
- Garfield D, Herbergs A & Davis P 2007 Re: hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *Journal of the National Cancer Institute* **99** 975–976. (doi:10.1093/jnci/djm008)
- Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, Zeold A & Bianco AC 2008 Cellular and molecular basis of deiodinase-regulated thyroid hormone signalling. *Endocrine Reviews* **29** 898–938. (doi:10.1210/er.2008-0019)
- Goodman VL, Rock EP, Dagher R, Ramchandani RP, Abraham S, Gobburu JV, Booth BP, Verbois SL, Morse DE, Liang CY et al. 2007 Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clinical Cancer Research* **13** 1367–1373. (doi:10.1158/1078-0432.CCR-06-2328)
- Hartmann JT, Haap M, Kopp HG & Lipp HP 2009 Tyrosine kinase inhibitors – a review on pharmacology, metabolism and side effects. *Current Drug Metabolism* **10** 470–481. (doi:10.2174/138920009788897975)
- Herbergs AA, Goyal LK, Suh JH, Lee S, Reddy CA, Cohen BH, Stevens GH, Reddy SK, Peereboom DM, Elson PJ et al. 2003 Propylthiouracil-induced chemical hypothyroidism with high-dose tamoxifen prolongs survival in recurrent high grade glioma: a phase I/II study. *Anticancer Research* **23** 617–626.
- Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA & Braverman LE 2002 Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism* **87** 489–499. (doi:10.1210/jc.87.2.489)
- Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD & Motzer RJ 2010 Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of pharmacokinetic/-pharmacodynamic meta-analysis. *Cancer Chemotherapy and Pharmacology* **66** 357–371. (doi:10.1007/s00280-009-1170-y)
- Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Stamoslawski E, Sosman J, McDermott D, Bodrogi I et al. 2007 Temsirolimus, interferon α , or both for advanced renal-cell carcinoma. *New England Journal of Medicine* **356** 2271–2281. (doi:10.1056/NEJMoa066838)
- Hurwitz H, Dowlati A, Savage S, Fernando N, Lasalvia S, Whitehead B, Suttle B, Collins D, Ho P & Pandite L 2005 Safety, tolerability and pharmacokinetics of oral administration of GW786034 in pts with solid tumors. *Journal of Clinical Oncology* **23** 195s (suppl; abstr 3012). (doi:10.1200/JCO.2005.10.017)
- Hutson TE, Davis ID, Machiels JH, de Souza PL, Baker K, Bordogna W, Westlund R, Crofts T, Pandite L & Figlin RA 2008a Predictive and prognostic factors in phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor. *Annals of Oncology* **19** viii187 (suppl 8; abstr 5780). (doi:10.1093/annonc/mdn510)
- Hutson TE, Davis ID, Machiels JH, de Souza PL, Baker K, Bordogna W, Westlund R, Crofts T, Pandite L & Figlin RA 2008b Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor. *Journal of Clinical Oncology* **26** 261s (abstr 5046).
- Illouz F, Laboureaux-Soares S, Dubois S, Rohmer V & Rodien P 2009 Tyrosine kinase inhibitors and modifications of thyroid function tests: a review. *European Journal of Endocrinology* **160** 331–336. (doi:10.1530/EJE-08-0648)
- Kamba T, Tam BY, Hashizume H, Haskell A, Sennino B, Mancuso MR, Norberg SM, O'Brien SM, Davis RB, Gowen LC et al. 2006 VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. *American Journal of Physiology. Heart and Circulatory Physiology* **290** H560–H576. (doi:10.1152/ajpheart.00133.2005)
- Kappers MH, van Esch JH, Smedts FM, de Krijger RR, Eechoute K, Mathijssen RH, Sleijfer S, Leijten F, Danser AH, van den Meiracker AH et al. 2011 Sunitinib-induced hypothyroidism is due to induction of type 3 deiodinase activity and thyroidal capillary regression. *Journal of Clinical Endocrinology and Metabolism* **96** 3087–3094. (doi:10.1210/jc.2011-1172)
- Kohrle J 2000 The selenoenzyme family of deiodinase isozymes controls local thyroid hormone availability. *Reviews in Endocrine & Metabolic Disorders* **1** 49–58. (doi:10.1023/A:1010012419869)
- Kollmannsberger C, Bjarnason G, Burnett P, Creel P, Davis M, Dawson N, Feldman D, George S, Hershman J, Lechner T et al. 2011 Sunitinib in metastatic renal cell carcinoma: recommendation for management of noncardiovascular toxicities. *Oncologist* **16** 543–553. (doi:10.1634/theoncologist.2010-0263)
- La Plant KD & Louzon PD 2010 Pazopanib: an oral multitargeted tyrosine kinase inhibitor for use in renal cell carcinoma. *Annals of Pharmacotherapy* **44** 1054–1060. (doi:10.1345/aph.1M251)
- Leese GP, Flynn RV, Jung RT, Macdonald TM, Murphy MJ & Morris AD 2008 Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS). *Clinical Endocrinology* **68** 311–316.
- Le Tourneau C, Faivre S & Raymond E 2008 New developments in multitargeted therapy for patients with solid tumours. *Cancer Treatment Reviews* **34** 37–48. (doi:10.1016/j.ctrv.2007.09.003)
- Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, Patard JJ, Mulders PF & Sinescu IC 2010 Guidelines on renal cell carcinoma. *European Urology*.
- Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A et al. 2008 Sorafenib in advanced hepatocellular carcinoma. *New England Journal of Medicine* **359** 378–390. (doi:10.1056/NEJMoa0708857)
- Lopez-Beltran A, Carrasco JC, Cheng L, Scarpelli M, Kirkali Z & Montironi R 2009 update on the classification of renal epithelial tumors in adults. *International Journal of Urology* **16** 432–443. (doi:10.1111/j.1442-2042.2009.02302.x)
- Makita N & Iiri T 2013 Tyrosine kinase inhibitor-induced thyroid disorders: a review and hypothesis. *Thyroid* **23** 151–159. (doi:10.1089/thy.2012.0456)
- Makita N, Miyakawa M, Fujita T & Iiri T 2010 Sunitinib induces hypothyroidism with a markedly reduced vascularity. *Thyroid* **20** 323–326. (doi:10.1089/thy.2009.0414)
- Mannavola D, Coco P, Vannucchi G, Bertuelli R, Carletto M, Casali PG, Beck-Peccoz P & Fugazzola L 2007 A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. *Journal of Clinical Endocrinology and Metabolism* **92** 3531–3534. (doi:10.1210/jc.2007-0586)
- Mathew A, Devesa SS, Fraumeni JF Jr & Chow WH 2002 Global increases in kidney cancer incidence, 1973–1992. *European Journal of Cancer Prevention* **11** 171–178. (doi:10.1097/00008469-200204000-00010)
- Matikainen T, Perez GI, Zheng TS, Kluzak TR, Rueda BR, Flavell RA & Tilly JL 2001 Caspase-3 gene knockout defines cell lineage specificity for programmed cell death signaling in the ovary. *Endocrinology* **142** 2468–2480. (doi:10.1210/en.142.6.2468)
- Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, Schreck RE, Abrams TJ, Ngai TJ, Lee LB et al. 2003 *In vivo* antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clinical Cancer Research* **9** 327–337.
- Miyake H, Kurahashi T, Yamanaka K, Kondo Y, Muramaki M, Takenaka A, Inoue TA & Fujisawa M 2010 Abnormalities of thyroid function in Japanese patients with metastatic renal cell carcinoma treated with

- sorafenib: a prospective evaluation. *Urologic Oncology* **28** 515–519. (doi:10.1016/j.urolonc.2009.08.011)
- Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE et al. 2006 Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *Journal of Clinical Oncology* **24** 16–24. (doi:10.1200/JCO.2005.02.2574)
- Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST et al. 2007 Sunitinib versus interferon α in metastatic renal-cell carcinoma. *New England Journal of Medicine* **356** 115–124. (doi:10.1056/NEJMoa065044)
- Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N et al. 2008 Efficacy of everolimus in advanced renal cell carcinoma: a double blind, randomised, placebo-controlled phase III trial. *Lancet* **372** 449–456. (doi:10.1016/S0140-6736(08)61039-9)
- Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA et al. 2009 Overall survival and updated results for sunitinib compared with interferon α in patients with metastatic renal cell carcinoma. *Journal of Clinical Oncology* **27** 3584–3590. (doi:10.1200/JCO.2008.20.1293)
- Motzer RJ, Hutson TE, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, De Souza P, Merchan JR, Fife K, et al. 2012 Randomised, open label. Phase III trial of pazopanib versus sunitinib in first-line treatment of patients with metastatic renal cell carcinoma (mRCC); results of the COMPARZ trial. Congress of the ESMO, September 28–October 2, 2012, Vienna (abstract 8LBA_PR).
- Nelson M, Hercborgs A, Rybicki L & Strome M 2006 Association between development of hypothyroidism and improved survival in patients with head and neck cancer. *Archives of Otolaryngology, Head & Neck Surgery* **132** 1041–1046. (doi:10.1001/archotol.132.10.1041)
- Oberg C, Li J, Pauley A, Wolf E, Gurney M & Lendahl U 2001 The Notch intracellular domain is ubiquitinated and negatively regulated by the mammalian Sel-10 homolog. *Journal of Biological Chemistry* **276** 35847–35853. (doi:10.1074/jbc.M103992200)
- Oetting A 2007 New insights into thyroid hormone action. *Best Practice & Research. Clinical Endocrinology & Metabolism* **21** 193–208. (doi:10.1016/j.beem.2007.04.004)
- O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW, Wong LM, Hong W, Lee LB, Town A et al. 2003 SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity *in vitro* and *in vivo*. *Blood* **101** 3597–3605. (doi:10.1182/blood-2002-07-2307)
- Rabinovitch RA, Zelefsky MJ, Gaynor JJ & Fuks Z 1994 Patterns of failure following surgical resection of renal cell carcinoma: implications for adjuvant local and systemic therapy. *Journal of Clinical Oncology* **12** 206–212.
- Ratain MJ, Eisen T & Stadler WM 2006 Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *Journal of Clinical Oncology* **24** 2505–2512. (doi:10.1200/JCO.2005.03.6723)
- Ries LAG, Melbert D, Krapcho M, et al. 2008 Editors SEER cancer statistics review, 1975–2005. National Cancer Institute.
- Riesenbeck LM, Biers S, Hoffmeister I, Köpke T, Papavasiliou P, Hertle L, Thielen B & Herrmann E 2011 Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. *World Journal of Urology* **29** 807–813. (doi:10.1007/s00345-010-0627-2)
- Rini BI 2009 Vascular endothelial growth factor-targeted therapy in metastatic renal cell carcinoma. *Cancer* **115** 2306–2312. (doi:10.1002/cncr.24227)
- Rini BI, Tamaskar I, Shaheen P, Salas R, Garcia J, Wood L, Reddy S, Dreicer R & Bukowski RM 2007 Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *Journal of the National Cancer Institute* **99** 81–83. (doi:10.1093/jnci/djk008)
- Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, Archer L, Atkins JN, Picus J, Czykowski P et al. 2008 Bevacizumab plus interferon α compared with interferon α monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *Journal of Clinical Oncology* **26** 5422–5428. (doi:10.1200/JCO.2008.16.9847)
- Rini BI, Wilding G, Hudes G, Stadler WM, Kim S, Tarazi J, Rosbrook B, Trask PC, Wood L & Dutcher JP 2009 Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *Journal of Clinical Oncology* **27** 4462–4468. (doi:10.1200/JCO.2008.21.7034)
- Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, Atkins JN, Picus J, Czykowski P, Dutcher J et al. 2010 Phase III trial of bevacizumab plus interferon α versus interferon α monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *Journal of Clinical Oncology* **28** 2137–2143. (doi:10.1200/JCO.2009.26.5561)
- Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, Michaelson MD, Gorbunova VA, Gore ME, Rusakov IG et al. 2011 Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* **378** 1931–1939. (doi:10.1016/S0140-6736(11)61613-9)
- Rivas M & Santisteban P 2003 TSH-activated signaling pathways in thyroid tumorigenesis. *Molecular and Cellular Endocrinology* **13** 31–45. (doi:10.1016/j.mce.2003.10.029)
- Rixe O, Bukowski RM, Michaelson MD, Wilding G, Hudes GR, Bolte O, Motzer RJ, Bycott P, Liao KF, Freddo J et al. 2007 Axitinib treatment in patients with cytokinerefractory metastatic renal-cell cancer: a phase II study. *Lancet Oncology* **8** 975–984. (doi:10.1016/S1470-2045(07)70285-1)
- Roberts CG & Ladenson PW 2004 Hypothyroidism. *Lancet* **363** 793–803. (doi:10.1016/S0140-6736(04)15696-1)
- Rugo HS, Stopeck AT, Joy AA, Chan S, Verma S, Lluch A, Liao KF, Kim S, Bycott P, Rosbrook B et al. 2011 Randomized, placebo-controlled, double-blind, phase II study of axitinib plus docetaxel versus docetaxel plus placebo in patients with metastatic breast cancer. *Journal of Clinical Oncology* **29** 2459–2465. (doi:10.1200/JCO.2010.31.2975)
- Sabatier R, Eymard JC, Walz J, Deville JL, Narbonne H, Boher JM, Salem N, Marcy M, Brunelle S, Viens P et al. 2012 Could thyroid dysfunction influence outcome in sunitinib-treated metastatic renal cell carcinoma? *Annals of Oncology* **23** 714–721. (doi:10.1093/annonc/mdr275)
- Salem AK, Fenton MS, Marion KM & Hershman JM 2008 Effect of sunitinib on growth and function of FRTL-5 thyroid cells. *Thyroid* **18** 631–635. (doi:10.1089/thy.2007.0336)
- Schiller JH, Larson T, Ou SH, Limentani S, Sandler A, Vokes E, Kim S, Liao K, Bycott P, Olszanski AJ et al. 2009 Efficacy and safety of axitinib in patients with advanced nonsmall-cell lung cancer: results from a phase II study. *Journal of Clinical Oncology* **27** 3836–3841. (doi:10.1200/JCO.2008.20.8355)
- Schmidinger M, Vogl UM, Bojic M, Lamm W, Heinzl H, Haitel A, Clodi M, Kramer G & Zielinski CC 2011 Hypothyroidism in patients with renal cell carcinoma: blessing or curse? *Cancer* **117** 534–544. (doi:10.1002/cncr.25422)
- Schöffski P, Dumez H, Clement P, Hoeben A, Prenen H, Wolter P, Joniau S, Roskams T & Van Poppel H 2006a Emerging role of tyrosine kinase inhibitors in the treatment of advanced renal cell cancer: a review. *Annals of Oncology* **17** 1185–1196. (doi:10.1093/annonc/mdj133)
- Schöffski P, Wolter P, Himpe U, Dychter SS, Baum C, Prenen H, Wildiers H, Bex M & Dumez H 2006b Sunitinib-related thyroid dysfunction: a single center retrospective and prospective evaluation. *Journal of Clinical Oncology* **24** 3092.
- Schwandt A, Wood LS, Rini B & Dreicer R 2009 Management of side effects associated with sunitinib therapy for patients with renal cell carcinoma. *OncoTargets and Therapy* **2** 51–61.
- Schwartz CE & Stevenson RE 2007 The MCT8 thyroid hormone transporter and Allan–Herndon–Dudley syndrome. *Best Practice & Research. Clinical Endocrinology & Metabolism* **21** 307–321. (doi:10.1016/j.beem.2007.03.009)

- Sella A, Hercbergs AH, Hanovich E & Kovel S 2012 Does sunitinib-induced hypothyroidism play a role in the activity of sunitinib in metastatic renal cell carcinoma? *Chemotherapy* **58** 200–205. (doi:10.1159/000337079)
- Shinohara N, Takahashi M, Kamishima T, Ikushima H, Otsuka N, Ishizu A, Shimizu C, Kanayama H & Nonomura K 2011 The incidence and mechanism of sunitinib-induced thyroid atrophy in patients with metastatic renal cell carcinoma. *British Journal of Cancer* **104** 241–247. (doi:10.1038/sj.bjc.6606029)
- Simonides WS, Mulcahey MA, Redout EM, Muller A, Zuidwijk MJ, Visser TJ, Wassen FW, Crescenzi A, da-Silva WS, Harney J et al. 2008 Hypoxia-inducible factor induces local thyroid hormone inactivation during hypoxic-ischemic disease in rats. *Journal of Clinical Investigation* **118** 975–983.
- Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salaman P, Gladkov OA, Kavina A et al. 2010 Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *Journal of Clinical Oncology* **28** 1061–1068. (doi:10.1200/JCO.2009.23.9764)
- Sukocheva OA & Carpenter DO 2006 Anti-apoptotic effects of 3,5,30-triiodothyronine in mouse hepatocytes. *Journal of Endocrinology* **191** 447–458. (doi:10.1677/joe.1.07061)
- Sulkes A 2010 Novel multitargeted anticancer oral therapies: sunitinib and sorafenib as a paradigm. *Israel Medical Association Journal* **12** 628–632.
- Tamaskar I, Bukowski R, Elson P, Ioachimescu AG, Wood L, Dreicer R, Mekhail T, Garcia J & Rini BI 2008 Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. *Annals of Oncology* **19** 265–268. (doi:10.1093/annonc/mdm483)
- Tomita Y, Uemura H, Fujimoto H, Kanayama HO, Shinohara N, Nakazawa H, Imai K, Umeyama Y, Ozono S, Naito S et al. 2011 Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: a phase II study in Japanese patients with cytokine-refractory metastatic renal cell carcinoma. *European Journal of Cancer* **47** 2592–2602. (doi:10.1016/j.ejca.2011.07.014)
- Torino F, Corsello SM, Longo R, Barnabei A & Gasparini G 2009 Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. *Nature Reviews. Clinical Oncology* **6** 219–228. (doi:10.1038/nrclinonc.2009.4)
- Trentin AG, Alvarez-Silva M & Moura Neto V 2001 Thyroid hormone induces cerebellar astrocytes and C6 glioma cells to secrete mitogenic growth factors. *American Journal of Physiology. Endocrinology and Metabolism* **281** E1088–E1094.
- Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T & Smith PA 1977 The spectrum of thyroid disease in a community: the Whickham survey. *Clinical Endocrinology* **7** 481–493. (doi:10.1111/j.1365-2265.1977.tb01340.x)
- Utiger RD 1965 Radioimmunoassay of human plasma thyrotropin. *Journal of Clinical Investigation* **44** 1277–1286. (doi:10.1172/JCI105234)
- Vakkalanka BK, Elson P, Wood L, Dreicer R, Garcia JA, Bukowski RM & Rini BI 2008 Long term toxicity of tyrosine kinase inhibitors (TKIs) in patients with metastatic clear cell renal cell carcinoma (RCC).
- 44th Annual Meeting of the American Society of Clinical Oncology (ASCO); Chicago, Illinois, May 30–June 3, 2008.
- Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H & Tunbridge F 1995 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. *Clinical Endocrinology* **43** 55–68. (doi:10.1111/j.1365-2265.1995.tb01894.x)
- Verga Falzacappa C, Panacchia L, Bucci B, Stigliano A, Gisella Cavallo M, Brunetti E, Toscano V & Misiti S 2006 3,5,30-Triiodothyronine (T₃) is a survival factor for pancreatic b-cells undergoing apoptosis. *Journal of Cellular Physiology* **206** 309–321. (doi:10.1002/jcp.20460)
- Verga Falzacappa C, Mangialardo C, Patriarca V, Bucci B, Amendola D, Raffa S, Torrisi MR, Silvestrini G, Ballanti P, Moriggi G et al. 2009 Thyroid hormones induce cell proliferation and survival in ovarian granulosa cells COV 434. *Journal of Cellular Physiology* **221** 242–253. (doi:10.1002/jcp.21849)
- Verga Falzacappa C, Timperi E, Bucci B, Amendola D, Piergrossi P, D'Amico D, Santaguida MG, Centanni M & Misiti S 2012 T₃ preserves ovarian granulosa cells from chemotherapy-induced apoptosis. *Journal of Endocrinology* **215** 281–289. (doi:10.1530/JOE-12-0153)
- Vetter ML, Kaul S & Iqbal N 2008 Tyrosine kinase inhibitors and the thyroid as both an unintended and an intended target. *Endocrine Practice* **14** 618–624. (doi:10.4158/EP.14.5.618)
- Wang JF, Milosveski V, Schramek C, Fong GH, Becks GP & Hill DJ 1998 Presence and possible role of vascular endothelial growth factor in thyroid cell growth and function. *Journal of Endocrinology* **157** 5–12. (doi:10.1677/joe.0.1570005)
- Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M et al. 2004 BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Research* **64** 7099–7109. (doi:10.1158/0008-5472.CAN-04-1443)
- Wolter P, Dumez H & Schöffski P 2007 Sunitinib and hypothyroidism. *New England Journal of Medicine* **356** 1580–1581. (doi:10.1056/NEJMc070327)
- Wolter P, Stefan C, Decallonne B, Dumez H, Bex M, Carmeliet P & Schöffski P 2008 The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. *British Journal of Cancer* **99** 448–454. (doi:10.1038/sj.bjc.6604497)
- Wong E, Rosen LS, Mulay M, Vanvugt A, Dinolfo M, Tomoda C, Sugawara M & Hershman JM 2007 Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. *Thyroid* **17** 351–355. (doi:10.1089/thy.2006.0308)
- Zhang C, Xia G & Tsang BK 2011 Interactions of thyroid hormone and FSH in the regulation of rat granulosa cell apoptosis. *Frontiers in Bioscience* **1** 1401–1413.
- Zygulska AL, Krzemieniecki K & Sowa-Staszczak A 2012 Hypothyroidism during treatment with tyrosine kinase inhibitors. *Endokrynologia Polska* **63** 302–306.

Received in final form 3 July 2013

Accepted 5 July 2013

Made available online as an Accepted Preprint

5 July 2013