Thyroid dysfunction and tyrosine kinase inhibitors in renal cell carcinoma

Loredana Bianchi, Luigi Rossi, Federica Tomao, 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

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

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. 2007). 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, Faiivre 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, Motzet 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.

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

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

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

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

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

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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, Schmider 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% (≤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 T₄ and T₃ 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 (Hercbergs 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 (T₃) 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 T₃ 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 T₃ 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 T₃, even when there is a tight activation signal triggered by paclitaxel (Verga Falzacappa et al. 2012). 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 (Sukocheva & Carpenter 2006).

As just highlighted, within the cell, T₃ is the more potent hormone, and the major pathway for the production of circulating T₃ is via 5'-deiodination of the outer ring of T₄ 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 T₃ 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;
HR 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 T4 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 antipapoptotic factor has been demonstrated in diverse cell systems and different pro- and antipapoptotic 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
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