The Emerging Role of Sunitinib in the Treatment of Advanced Epithelial Thyroid Cancer: Our Experience and Review of Literature

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Abstract: Tyrosine kinase receptors have been shown to play an important role in epithelial thyroid tumor growth and angiogenesis. Thyroid cancers commonly present oncogene mutations involved in MAPK kinase pathway like BRAF and RET; they are also frequently dependent on VEGF stimuli. Preliminary clinical experiences suggest a promising role of sunitinib (a tyrosine kinase inhibitor) for the treatment of advanced thyroid cancers. This review deals with the available data on the effect of sunitinib in the treatment of metastatic, radioiodine refractory thyroid cancers. We also report our experience with the off-label use of sunitinib in such patients.

Keywords: Thyroid cancer, sunitinib, tyrosin-kinase inhibitor, metastatic disease.

INTRODUCTION

About 10–20% of adult patients with differentiated thyroid cancer (DTC) will develop distant metastases [1], at least half of which will not respond to conventional therapy such as radioactive iodine (RAI) and TSH suppressive therapy with levothyroxine. Relative survival is encouraging for adult patients diagnosed under age 45 with distant metastases (stage II), while it steadily declines when the same diagnosis is done after age 45 (stage IV). Indeed, in observational studies (mostly referred to adults) of patients with stage IV cancer, long-term survival is about 43%, compared with 86% of those with low risk disease (stage I – II) [2-4]. In patients with radioactive iodine (RAI) resistant disease, the long-term overall survival drops to 10% [5], and conventional chemotherapy response rate is typically 25% or less, at the expense of marked toxicity [6].

Tyrosine kinase receptors play an important role in tumor growth and angiogenesis [7-8]. These molecules affect tumor growth and tumor cells survival directly through the inhibition of both intracellular signaling pathways and neoangiogenesis process. Thyroid tumors frequently present oncogene mutations involved in mitogen-activated protein kinase (MAPK) pathway like BRAF and RET. Thyroid cancers are also dependent on vascular endothelial growth factor (VEGF) stimuli [9-10], and targeting of VEGF and other members of the signaling cascade responsible for neoangiogenesis may limit cancer growth by restricting blood supply.

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Several early-phase clinical trials for testing the activity and tolerability of various tyrosine kinase inhibitors (TKI) are currently ongoing. Although no TKI agent has been approved for the treatment of thyroid cancer, bearing in mind preliminary clinical results, the National Comprehensive Cancer Center Network (NCCN) guidelines recommend consideration of TKI agents in patients with progressive, radioiodine refractory DTC who are not willing or able to enter into a clinical trial.

Sunitinib (Sutent, Pfizer, Inc., New York, NY; SU11248) is a novel tyrosine kinase inhibitor, approved in 2006 by Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors. The drug has been shown to be safe and effective for the treatment of various other cancers with either direct anti-tumor or anti-angiogenic effects [11-13].

This review will describe the role of sunitinib in the treatment of advanced epithelial thyroid cancer, unresponsive to RAI. We will also report our preliminary experience with the off-label use of sunitinib in patients with metastatic, refractory DTC.

RATIONALE

Sunitinib (Fig. **1**), synthesized by SUGEN, Inc. ZD1839, is a selective small molecule inhibitor of tyrosine kinase activity [14]. Sunitinib malate is described chemically as butanedioic acid, hydroxy-, (2S)-, compound with *N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-ylidine)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ and the molecular weight is 532.6 Daltons.

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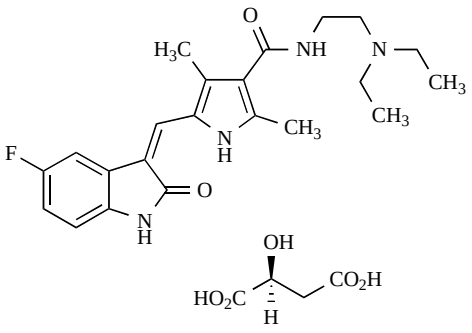

Fig. (1). Chemical structure of sunitinib.

Sunitinib has been shown to inhibit VEGF-1–3, receptors platelet-derived growth factor receptor (PDGFRα and PDGFRß), stem cell growth factor receptor (KIT), FMS-like tyrosine-kinase 3 (FLT3), and RET [15]. Sunitinib like other TKIs interfere with ATP binding site of kinase receptors. Both *in vitro* and *in vivo* studies have demonstrated that sunitinib is able to exert antitumor activity either directly against tumor cells by tyrosine-kinase receptor pathways or indirectly by the inhibition of angiogenesis [11-13].

During the past decade, several trials have been carried out for testing novel biologically targeted therapies for advanced thyroid carcinomas. Preclinical and clinical experiences indicate that oncogenic mutations are of primary importance for thyroid tumor development and growth [16-17]. As demonstrated from various tumor models most papillary thyroid cancers (PTCs) may be driven in part through single activating somatic mutations [18], and 80% of PTCs present mutation in genes encoding signaling up-stream of MAPK pathways [19]. As suggested by Flescher *et al.* [20], PTCs might become irrevocably addicted to the oncogenes that initiated tumorigenesis. Among the genetic alterations identified, etiologic rearrangements in the gene encoding RET (1-3) as well as activating mutation of Ras and point mutations of the gene encoding the BRAF serine/threonine kinase, are present in PTCs, with an overall prevalence higher than 70% [21-22]. Oncogenic rearrangements of RET (RET/PTCs) also occur with an incidence of 5–30% in spontaneous cases and 60–70% in radiation-induced PTC, with significant geographic variation [23]. RET/PTC rearrangement was found in PTC cell line 1 [24], resulting in constitutively active autophosphorylation of RET Y1062 that enhances the activation of STAT3 (signal transducer and activator of transcription 3) and promotes the reduction of sodium-iodide symporter (NIS) gene expression, a molecule concentrating iodide in the thyroid gland [25-26].

Kim *et al*. [27] evaluated the effect of sunitinib on PTC cell lines with genetic rearrangement of the RET gene and investigated the level of inhibition of the oncogenic RET/PTC tyrosine kinase. Results of this study show that sunitinib strongly inhibits RET/PTC kinase activity and exerts a powerful growth inhibitory effect. NIS is functional in many differentiated thyroid cancers but non-functional in about one-fourth of thyroid carcinomas, resulting in poor prognosis [28]. NIS expression is regulated by a complex mechanism; many transcription factors are involved and intracellular signaling pathway cross-talks, such as the MEK/ERK and AKT/PI3K pathways, appear to play an important role in NIS expression [29]. Fenton *et al.* [30] investigated the effect of sunitinib in RET/PTC-1 rearrangement cells by focusing on signal transduction pathways and NIS gene expression. The study confirms that sunitinib is a powerful inhibitor of RET/PTC associated thyroid cancers and could be used to enhance levels of active NIS protein for radioiodine uptake and cancer cell ablation [30].

Angiogenesis plays a critical role in supporting tumor cell growth and metastasis [31]; indeed, increased expression of angiogenic factors and high vascular density characterize tumors with invasive and metastatic features [32]. Marked angiogenic activity is a common feature of thyroid cancers, especially larger tumors as well as follicular cancers. As demonstrated by Giatromanolaki *et al.* [32] VEGF binding to VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR), leads to the activation of MAPK pathway thus promoting angiogenesis [33]. Moreover, the intensity of VEGF expression in PTC correlates with a higher risk of metastasis and recurrence, a shorter disease-free survival, and BRAF mutation status [34-35].

CLINICAL EXPERIENCES

The effectiveness of sunitinib on advanced, refractory thyroid cancers is still under investigation; the results of the main available clinical trials and the preliminary experiences are herewith reported. Cabanillas *et al*. [36] evaluated the off-label use of sunitinib and sorafenib, another TKI agent with antiangiogenic activity, in 31 adult patients with metastatic, radioiodine-refractory DTC. They alternatively employed a single agent sorafenib or sunitinib, and both the drugs appeared to be effective. The major responses occurred in the lung in contrast with minimal changes in nodal metastases and partial response in pleural and bone metastases, suggesting a tissue-specific response to TKI therapies [36].

Cohen *et al*. [37] carried out a phase II study on adult patients with medullary thyroid cancer (MTC) or DTC, refractory to standard treatments with evidence of progressive disease. Forty-three subjects (37 DTC, 6 MTC) were enrolled, 34 of whom received prior RAI and 6 prior systemic chemotherapy; treatment consisted of 6-week cycles of sunitinib 50 mg QD on a 4-week on/2-week off schedule. Thirty-one evaluable DTC patients completed 2 cycles, partial response or stabilization of disease being obtained in 13% and 68% of the cases, respectively. Ravaud *et al.* [38] recently reported the preliminary results of an ongoing phase II study in patients with medullary as well as differentiated or anaplastic thyroid cancer. Sunitinib was administered at 50 mg QD for 4 weeks every 6 weeks. Seventeen patients were enrolled while 15 of them were evaluable for clinical RECIST response [39]: 12 patients had stable disease, two showed partial responses (1 patient with almost 90% decrease of serum thyroglobulin level) and one a dramatic decrease of symptoms. Finally, an interesting clinical experience was recently reported by Carr *et al.* [40] who assessed the activity of sunitinib continuous dosing (37.5 mg) in patients with FDG-PET avid and RAI resistant

DTC or MTC. The primary end-point was response rate per RECIST criteria, while the secondary end-points included toxicity, overall survival, and time to progression. Response of FDG-PET analysis was also performed after 7 days of treatment. Thirty-five patients were enrolled (7 MTC; 28 DTC), and 33 patients were evaluated for disease response. Objective response was obtained in 11 patients (1 complete and 10 partial responses) and stabilization of disease in 15, while progression of disease was observed in the remaining 7 patients. The median time to progression was 12.8 months and (18)F-fluorodeoxyglucose (FDG)- positron emission tomography (PET), repeated on 22 patients, revealed that the median percent change in average SUVs was -11.7%, -13.9%, and +8.6% for patients with RECIST response, stable disease and progressive disease, respectively. The most common toxicities included fatigue, leucopenia with altered blood formula (neutropenia), hand/foot syndrome and diarrhea. One patient on anticoagulation died for gastrointestinal bleeding.

The above reported encouraging preliminary results, also according to NCCN guidelines, have prompted many physicians to prescribe sunitinib off-label in selected advanced thyroid carcinoma patients who cannot participate or be enrolled into ongoing clinical trials.

In this setting, our experience consists of the off-label treatment with sunitinib of 4 patients (two women and two men) with advanced DTC refractory to RAI (Table **1**). Patients were treated for at least 9 months (14.8±5.6 months, mean±SD); clinical response was assessed by serum thyroglobulin level measurement (every three months) as well as imaging evaluation (every six months or on oncologist judgment). All the patients started sunitinib at 50 mg daily dose with a treatment cycle of 4 weeks on and 2 weeks off, and were followed by a multidisciplinary team composed by an oncologist, an endocrinologist and a pharmacologist. Patients were invited to undergo periodic medical visits and clinical chemistry exams to control the treatment safety profile and disease evolution. Overall, so far we documented partial response in one patient with substantial regression of lymph node, lung and liver metastases, progression disease (bone metastasis) in one patient and stable disease along with marked improvement of clinical symptoms in the other two patients (Table **1**). The peculiar clinical pictures of these last two patients are hereby described.

Patient#1 had disseminated disease (cervical vertebra, occipital condyle, sternum and lung) with symptoms characterized by diffuse paresthesia of the right forehand and functional deficit of the ipsilateral hand, making the patient unable to write. At 12 and 18 months control, PET-CT demonstrated the reduction or substantial stability of cervical lesions along with complete response of lung metastases (Fig. **2A-B**). Starting from the 6th month of treatment, the patient referred a progressive improvement of neurological symptoms with complete recovery of the right hand function at 12 months follow-up. It is noteworthy that, during 2 months of subsequent sunitinib treatment withdrawal for difficulties in drug supply (delayed authorization for Healthcare reimbursement), the patient experienced a transient worsening of neurologic symptoms of the right hand followed by prompt recovery of both function and sensibility after sunitinib restart.

Patient#2 with metastatic PTC affecting the cervical region (surgically removed), lumbar column, cranial base, larynx and lung, underwent several RAI treatments as well as chemotherapy (vinorelbine and 5-fluorouracile) without any clinical response. One year of sunitinib therapy induced a partial disease response with disappearance of the laryngeal lesion (Fig. **3**) and substantial reduction of the cranial base lesions associated to relief of chronic headache. Interestingly, a marked decrease of serum thyroglobulin levels after an initial transient peak, probably due to massive lysis of tumor cells, was observed (Fig. **4**).

Sunitinib therapy resulted free of significant drawbacks during the first 3-4 months of treatment in all the patients while fatigue, hypertension (worsening of blood pressure control by current treatment), diarrhea, mucosal aphthae, headache, hematologic toxicity (macrocytosis) and amenorrhea were experienced thereafter, mainly at the end treatment cycle. The lack of specific guidelines for the management of long term side effects of sunitinib in thyroid

Table 1. Clinical and Pathological Features of Thyroid Cancer Patients Treated with Sunitinib

Patient	Gender	Age at diagnosis (years)	Pathological diagnosis	Pathologic stage	Previous Chemotherapy	RAI	Restaging at sunitinib start	Age at sunitinib start (years)	Clinical response	Follow-up (months)
1	F	40	FTC	pT4, N1, Mx	no	yes	N1b, M1 (lung, bone)	48	SD	22
2	M	48	PTC	pT4, N1, Mx	yes	yes	N1b, M1 (lung, bone)	61	SD	16
3	F	59	FTC	pT4, N1, Mx	no	yes	N1b, M1 (lung, liver)	70	PR	9
4	M	48	PTC	pT4, N1, M1	no	yes	N1b, M1 (lung, bone)	55	PD	12

RAI: radioactive iodine; FTC: follicular thyroid cancer; PTC: papillary thyroid cancer; SD: stable disease; PR: partial response; PD: progressive disease.

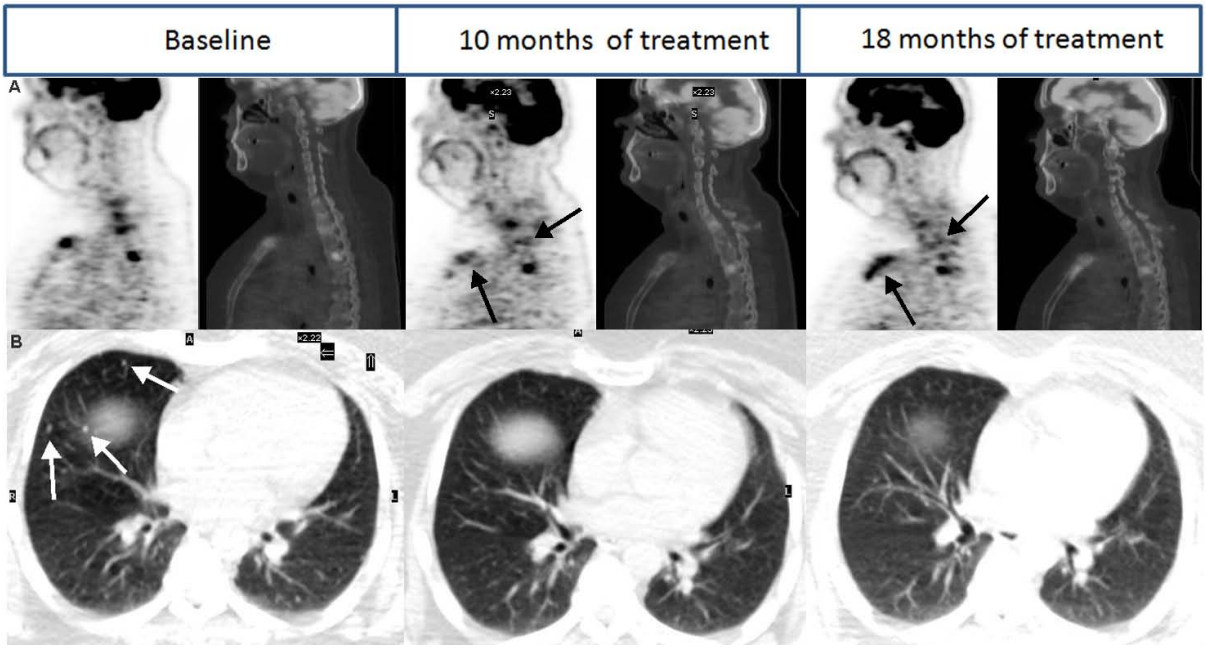

Fig. (2). Cervical vertebra and sternum metastases as assessed by TC/PET (panel **A**) at baseline, after 10 months and after 18 months of sunitinib therapy. Lung metastases as assessed by TC (panel **B**) at the same time course. Changing lesions are indicated by arrows.

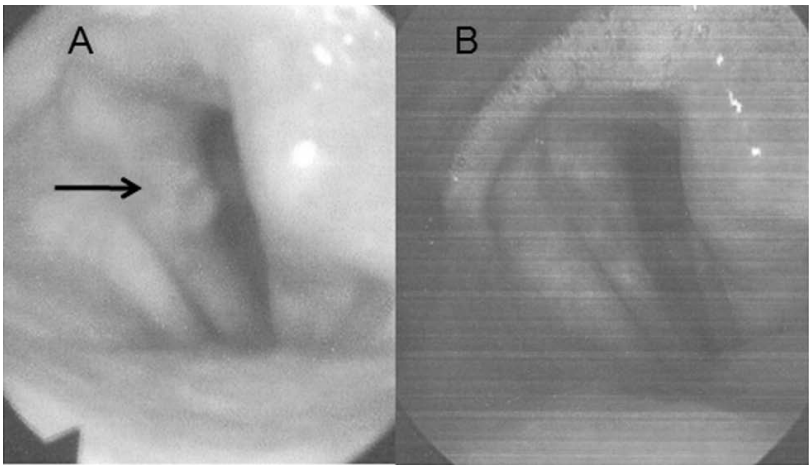

Fig. (3). Complete resolution of laryngeal lesion (arrow, panel **A**) after one year of sunitinib treatment (panel **B**).

cancer patients and the scarce published clinical experiences that are mainly represented by early phase trials, made the clinical decision complex and essentially based on previous experiences in registrative clinical trials of other cancers. In this setting, a recent meta-analysis, including 639 patients with renal cell carcinoma, showed a clear dose-response relationship for sunitinib [41]. Indeed, patients with the highest exposure to the drug displayed longer time-to-progression, longer overall survival, a higher probability of a response, and greater tumor size decreases. The analysis highlighted the importance of maintaining patients on a 50-mg dose of sunitinib and striving to avoid unscheduled dosing interruptions or titration during treatment. However, in those patients for whom it may not be possible to maintain a full dose, the authors not excluded the use of alternative dosing schedules, as employed in some studies. According to these considerations and personal clinical experience, our oncologist managed in the same way thyroid cancer patient adverse events, reserving alternative-dosing schedule in those patients with good clinical response in the face of severe side affects. This strategy allowed the patients to benefit from long-term sunitinib therapy.

SAFETY PROFILE

Sunitinib is endowed by a tolerability profile similar to other antiangiogenic agents. Adverse events reported in large series of patients with renal cell carcinoma are a variety and include fatigue, hematologic toxicity, hypothyroidism, cardiovascular toxicity (including hypertension), gastrointestinal toxicity, dermatologic changes (including hand–foot syndrome) and tumor lysis syndrome [42-43].

Hematologic toxicities were not uncommon in patients who received sunitinib for various kinds of tumors [42-43]. All grade of neutropenia, anemia, and thrombocytopenia occurred in 60–70% of patients treated with this agent, but

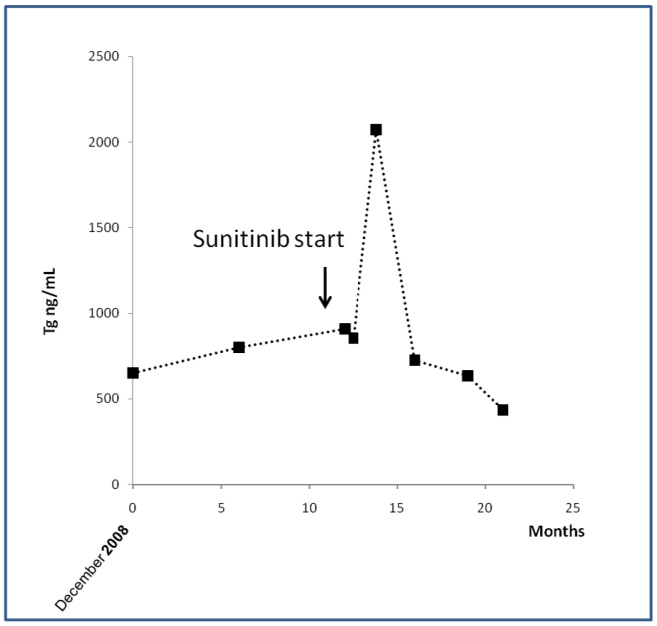

Fig. (4). Serum thyroglobulin levels in a man with advanced, metastatic thyroid cancer before and after sunitinib therapy (treatment start is indicated by arrow).

grade 3 or 4 toxicity was seldom observed [43]. Since few studies of early phases (small number of patients) have been conducted to detect the safety profile of sunitinib in advanced thyroid cancer patients, and most of these patients have been previously treated with radiation, the effect of sunitinib on the hematopoietic system should be further assessed in large clinical trials [44]. In this setting, the short-term hematologic toxicity of sunitinib in advanced DTC was assessed retrospectively in 6 patients with DTC and 4 with MTC, by measuring red cell and platelet mass as well as the leukocyte formula. Despite normal circulating folate and cobalamin levels, all the patients presented macrocytosis and almost 50% reduction of monocyte count, but no high-grade lymphocytopenia was observed [45].

Hypothyroidism is frequently observed in patients treated with sunitinib, and in prospective studies it has been reported in 36–71% of patients receiving this drug [46]; in some patients, sunitinib induced hyperthyroidism as well [47]. Although several hypotheses have been proposed so far to explain this side effect, the exact mechanism is still unknown. Both hypothyroidism and hyperthyroidism may be caused by destructive thyroiditis, but other mechanisms such as interference of sunitinib with thyroid iodine organification have been suggested [48]. Wong *et al*. [49] reviewed 89 cases of patients taking sunitinib for 1–48 months for various tumors. Twenty-one out of 40 (53%) patients tested for thyroid function after starting sunitinib, developed subclinical hypothyroidism (increased serum TSH value in the face of normal free thyroid hormone levels). In order to better understand the effect of sunitinib on intra-thyroidal iodine metabolism the authors measured thyroid peroxidase (TPO) activity by two different assay systems: guaiacol oxidation and protein iodination. TPO inhibition by sunitinib was revealed by both methods, with a potency of 25–30% of that of propylthiouracil. Moreover, because an increased need of thyroxine therapy is frequently observed in athyreotic patients treated with tyrosine kinase inhibitors, the pathogenesis of hypothyroidism might also include alterations in peripheral thyroid hormone metabolism. Stepwise deiodination is the major route of thyroid hormone degradation and is mediated by iodothyronine deiodinases (D1, D2, and D3). On this basis, Abdulrahman *et al*. [48] evaluated the effects of sorafenib, another antiangiogenic TKI which may cause hypothyroidism, in 32 athyreotic patients. To assess the effect of sorafenib on iodothyronine deiodination, serum T3/T4 and T3/rT3 ratios were calculated: a higher substitution dose of thyroxine was needed to maintain serum FT4 levels and serum T3/T4 and T3/rT3 ratios decreased by 18 and 22%, respectively in accordance with the hypothesis of peripheral hormone alteration [48]. In particular, these data suggest that sunitinib might enhance the deiodinase 3 function resulting in increased catabolism of free thyroid hormones. These findings are consistent with a previous report in which eight imatinib treated patients who had undergone thyroidectomy required substantial increase in levothyroxine replacement dose to maintain euthyroidism [50]. Until now, however, no data are available on possible sunitinib induced hypothyroidism in athyreotic patients.

Sunitinib is metabolized in the liver by cytochrome P450 (CYP3A4) pathway; thus, drugs that affect the CYP3A4 pathway might alter the metabolism of sunitinib and influence its serum level. Therefore, caution should be used when sunitinib is administered in patients receiving CYP3A4 inhibitors, an association which may result in increased serum concentrations of the drug. Conversely, coadministration with CYP3A4 inducers may lead to lower sunitinib levels and potentially decrease its therapeutic efficacy. Indeed, ketoconazole (cytochrome inhibitor) administration to healthy volunteers increased the cumulative exposure of sunitinib while rifampicin (cytochrome inducer) co-administration resulted in decreased systemic exposure [51-53].

Sunitinib essentially elicits side affects by two mechanisms: “on-target” or “mechanism-dependent” toxicity and “off-target” or “mechanism-independent” toxicity [54]. Due to its multi-target activity directed to both host tissues and tumor cells, sunitinib presents various side effects involving different apparatus and, it makes difficult to distinguish the precise pathogenesis of each adverse event. Cardiovascular toxicity might represent a suitable model of both on-target and off-target side effects caused by anti-vascular drugs. Sunitinib therapy is associated with hypertension and cardiac toxicity, of which the underlying pathophysiological mechanism is not well understood [55]. In this setting, two recent clinical studies in patients treated for gastrointestinal stromal tumors or renal cell carcinoma have evidenced sunitinib-associated cardiotoxicity as revealed by heart failure and hypertension [55-57]. In order to assess the possible pathogenesis of such hemodynamic alterations, Kappers *et al*. [55] tested the effect of sunitinib on blood pressure, serum endothelin-1 levels, coronary microvascular function, cardiac structure, and cardiac mitochondrial function in an animal model. Eight days of

sunitinib administration induced a ≈30-mmHg rise in blood pressure, an attenuation of its circadian rhythm, and a 3-fold rise in serum endothelin-1 and creatinine, of which all reversed after sunitinib withdrawal, except for creatinine increase. Such data suggest that sunitinib induces a reversible rise in blood pressure associated with activation of the endothelin-1 system, suppression of the renin-angiotensin system, and generalized microvascular dysfunction. These alterations might account for sunitinib cardiovascular toxicity derived by specific endothelial VEGFR inhition (on-target side effect). Hasinoff *et al*. [58] using a rat myocyte model, investigated *in vitro* various mechanisms that might be responsible for sunitinib cardiotoxicity. Giving that myocytes exposed to sunitinib at concentrations corresponding to therapeutic levels presented a dose-dependent damage, documented by increased lactate dehydrogenase (LDH) level into the medium of cell culture, they suggested a direct cytotoxic activity of the drug (off-target side effect).

CONCLUSIONS

The long-term overall survival of patients with advanced, RAI-resistant thyroid tumors is less than 10% [5], thus favoring the development of new targeted therapy such as TKIs. The promising results obtained with these drugs, suggesting a possible tissue-specific response, have induced many physicians to administer sunitinib in an off-label manner [36]. Accordingly, even if TKI agents have been not approved for the treatment of thyroid tumors, international guidelines recommend consideration of small-molecule kinase inhibitors in selected cases. On this basis, sunitinib might represent a valid option for treatment of metastatic thyroid cancer when no other options are available. It should be underlined that, when patients are treated with new compounds like sunitinib, it is mandatory not only to focus on the possible benefits of the treatment, but also on the potential side effects and toxicities that may be common and, in some circumstances, severe. Indeed, the frequent onset of adverse events during therapy with TKI agents may potentially limit treatment continuation. Therefore, the management of DTC patients treated with sunitinib or other TKI agents needs a strict collaboration between specialists, particularly endocrinologists and oncologists. In our experience, beside conventional preventive strategies, a satisfactory tolerability of the drug was also obtained by alternative dosing schedules, although this finding requires verification in randomized, large clinical trials.

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