ORIGINAL ARTICLE

SUNITINIB, A VEGFR RECEPTOR TYROSINE KINASE INHIBITOR AND ITS THYROID EFFECTS

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Abstract

Thyroid dysfunction occurs in 14 - 85% of patients treated with sunitinib, a multitargeted tyrosine-kinase inhibitor. Twenty-nine patients (20 males/9 females) treated with sunitinib (median dose 50 mg/day, 4 weeks "on", 2 weeks "off" treatment regimen) for metastatic renal cell carcinoma were diagnosed with sunitinib-induced thyroid dysfunction. Thyroid function tests (thyroid-stimulating hormone (TSH), free T_4 (thyroxine)) were measured by chemiluminescence. Primary hypothyroidism was initially diagnosed in 25 patients (86.2%), while transient thyrotoxicosis occurred in 4 patients (13.8%), followed by persistent hypothyroidism. Median duration of sunitinib treatment till diagnosis of hypothyroidism was 7 months and of thyrotoxicosis of 6.5 months, respectively. Overt hypothyroidism (17/25 patients) prevailed over subclinical hypothyroidism (8/25 patients), while overt thyrotoxicosis occurred similarly with subclinical thyrotoxicosis (2/4 patients). Due to high prevalence of sunitinib-induced thyroid dysfunction, monitoring of thyroid function is recommended.

Rezumat

Disfuncţiile tiroidiene apar la 14-85% dintre pacienţii trataţi cu sunitinib, un inhibitor de tirozin-kinază care blochează mai mulţi factori de creştere. Douăzeci şi nouă de pacienţi (20B/9F) trataţi cu sunitinib (doza mediană 50 mg/zi, în cure de 4 săptămâni, apoi 2 săptămâni pauză) pentru carcinom renal, cu celulă clară, metastatic au fost diagnosticaţi cu distiroidii induse de sunitinib. Testele funcţionale tiroidiene (hormonul de stimulare tiroidiană (TSH), tiroxina liberă) au fost realizate prin chimiluminescenţă. Hipotiroidismul primar a fost diagnosticat la 25 pacienţi (86,2%), în timp ce 4 pacienţi (13,8%) au dezvoltat tireotoxicoză tranzitorie, urmată ulterior de hipotiroidism permanent. Mediana duratei de tratament cu Sunitinib până la diagnosticarea hipotiroidismului a fost de 7 luni şi a tireotoxicozei de 6,5 luni. Hipotiroidismul clinic manifest (17/25 pacienţi) a prevalat asupra hipotiroidismului subclinic (8/25 pacienţi), în timp ce tireotoxicoza a fost în egală măsură subclinic şi clinic manifestă (2/4 pacienţi). Datorită prevalenţei crescute a disfuncţiilor tiroidiene induse de sunitinib, se impune o monitorizare a funcţiei tiroidiene la pacienţii trataţi.

Keywords: VEGFR, sunitinib, thyroid dysfunction, renal cell carcinoma

Introduction

Antiangiogenic therapies inhibiting the vascular endothelial growth factor (VEGF) and mammalian target of rapamicin (mTOR) are standard treatments for metastatic renal cell carcinoma [15, 18]. Tyrosine kinase inhibitors (TKIs) targets different growth factor receptors (VEGFR 1-3, c-KIT, PDGFR α, β, FLT3, RET) and inhibits tumour growth, angiogenesis and metastatic invasion [14]. Side effects of TKIs includes skin reaction, nausea and vomiting, diarrhoea [12], fatigue, febrile neutropenia, thrombocytopenia [15], stomatitis [19], interstitial pneumonitis [23], hepatic toxicity [34], QT interval prolongation, hypertension [37], thyroid dysfunction and adrenal insufficiency [46], clinical features increased in chronic kidney disease patients (undergoing or not dialysis).

Thyroid dysfunction is a frequent side effect (8 - 85%) of TKIs. Meta-analysis of 12 trials (six on suninitib, four on cediranib, two on axitinib) showed that relative risk for developing all-grade hypothyroidism was 3.59 [2].

Sunitinib, an oral agent, is one of the first-generation TKIs, which targets multiple receptor tyrosine kinases, including vascular endothelial growth factor receptor; maximum plasma concentration of sunitinib occurred 6 - 12 hours after oral administration; its primary active metabolite is SU 12662. Half-life of sunitinib is 40 - 60 hours and of SU 12662 is 80 - 110 hours. Steady-state concentration of both sunitinib and SU 12662 are achieved in 10 - 14 days [27]. When administered in 4/2 schedule, sunitinib 50 - 100 mg daily for 28 days lead to 3 - 5.5 fold accumulation of the molecule and to 7 - 15 fold accumulation of

SU 12662, when compared with the first day of treatment [20, 27, 39].

The recommended dose in metastatic renal cell carcinoma (mRCC) is 50 mg daily for 4 weeks, followed by 2 weeks off treatment; however, an alternative 2 weeks on, followed by 1 week off schedule, seems to have better tolerability (no grade 4 toxicities and less than 30% patients with grade 3 toxicities) and similar efficacy [27, 43].

Sunitinib lead to thyroid dysfunction in 14 - 85% of treated patients [8, 17, 25, 28]. Is was associated especially with hypothyroidism [14], thyrotoxicosis also being reported, usually preceding hypothyroidism [26].

TKIs can induce thyroid dysfunction by various mechanisms: inhibition of VEGFR receptor (VEGFR2, VEGFR1) and platelet-derived growth factor receptor (PDGFR2) followed by capillary dysfunction and direct involution of the thyroid [31], thyroid autoimmunity (debated) [4, 5, 36], inhibition of iodine uptake and inhibition of thyroid peroxidase (TPO) activity, inhibition of monocarboxylate transporter 8 (MCT8), followed by impaired thyroid hormone (TH) trans-membrane transport, impaired thyroid hormone uptake in gastrointestinal tract, increased type 3 deiodinase activity with increased inactivation of TH [32], reduced TSH clearance, decrease of T_3 and/or T_4 inhibition of pituitary MCT8; negative effect on pituitary capillaries [3, 8, 25].

Materials and Methods

Patients

Medical files of twenty nine patients (20 males *vs* 9 females) with pathologically proven mRCC, treated with tyrosine kinase inhibitors (TKIs), who developed TKI-induced thyroid dysfunction were retrospectively reviewed. Between 2014 and 2016, patients were referred by oncologists from "Al. Trestioreanu" Institute of Oncology, Bucharest, Romania, to endocrinologists from "C. I. Parhon" National Institute of Endocrinology (tertiary oncology and endocrinology centres, respectively), when symptoms and/or signs of thyroid dysfunction occurred or abnormal thyroid function tests were detected. Patients were treated with sunitinib 50 mg/day, 4 weeks "on", 2 weeks "off" schedule.

Methods

Third generation TSH test was employed by a solid-phase, two-site chemiluminescent immunometric assay, using IMMULITE 2000 System analyser Siemens; normal range: 0.4 - 4 μIU/mL, analytical sensitivity: 0.004 μIU/mL. Free T_4 (FT4) was measured by a direct test - solid-phase, enzyme-labelled chemiluminescent competitive immunoassay (free T_4 in the sample competes with enzyme conjugated T_4 in the reagent for a limited number of antibody binding sites of the solid phase), also using IMMULITE 2000 System analysers Siemens. The solid phase was coated with monoclonal murine anti-T_4 antibody; the liquid phase consisted of alkaline phosphatase (bovine calf intestine) conjugated to T_4. Unbound patient sample and enzyme conjugate were removed by centrifugal washes. Finally, chemiluminescent substrate was added and the signal was generated proportionally to the bound enzyme; normal range: 0.89 - 1.76 ng/dL (11.5 - 22.7 pmol/L); analytical sensitivity 0.11 ng/dL (1.42 pmol/L). TPO antibodies were measured by a solid-phase, enzyme-labelled, chemiluminescent sequential immunometric assay, using the same analyser mentioned above; normal levels < 35 IU/mL; analytical sensitivity 5 IU/mL. Thyroglobulin was measured by a solid-phase, chemiluminescent immunoradiometric assay, using the same analyser; normal range: 0 - 10 ng/mL, analytical sensitivity 0.2 ng/mL.

Thyroid morphology and dimensions were assessed by ultrasound; ^{131}I radioiodine uptake (RAIU) was performed in two patients presenting overt thyrotoxicosis.

Statistical analyses

Data are presented as mean ± standard deviation and range (when appropriate) or median (25^{th} percentile, 75^{th} percentile). Survival analysis was performed using the Kaplan-Meier method. Relevant parameters were studied for influence on survival by univariate analysis using the log-rank test. Results were considered significant at the 0.05 level. Statistical analyses was performed using SPSS version 21.0.

Results and Discussion

Mean age of the studied patients at diagnosis of thyroid dysfunction was 59.97 ± 12.17 years, range 29 - 85 years. Metastases localization was: pulmonary (n = 22), bone (n = 7), adrenal (n = 4), liver (n = 3), brain (n = 2), 9 patients showed multiple sites metastases.

Median duration of TKI treatment till diagnosis of thyroid dysfunction was 7 months (25^{th} percentile: 5 months, 75^{th} percentile: 14 months, range: 1.5 - 66 months) as shown in Figure 1.

Primary hypothyroidism was initially diagnosed in 25 patients (86.2%), 18 M/7 F, aged 60.48 ± 12.3 years. Median duration of TKI treatment till diagnosis of primary hypothyroidism was 7 months (25^{th} percentile: 5 months, 75^{th} percentile: 15 months, range 1.5 - 66 months). Median TSH at diagnosis was 18.5 mIU/L (25^{th} percentile: 7 mIU/L, 75^{th} percentile: 39.36 mIU/L, range 4.95 - 395). Subclinical hypothyroidism (TSH > 4.5 mIU/L, normal FT_4 levels) was diagnosed in 8 patients (TSH range: 4.95 - 7.71 mIU/L), while overt hypothyroidism was diagnosed in 17 patients (TSH range: 12.24 - 395 mIU/L). TPO antibodies were negative in all patients, but one (TPO Abs =

778 IU/mL), who previously received interferon treatment.

The majority of patients showed thyroid gland atrophy. Three patients with hypothyroidism showed thyroid nodules larger than 2 cm; in one patient, pathology exam performed after total thyroidectomy revealed diffuse sclerosing variant of papillary thyroid carcinoma; in other patient with a 30/18 mm thyroid nodule TIRADS 3, cytological exam performed after fine needle aspiration biopsy revealed Bethesda III features and thyroid surgery was pending; the third patient refused fine needle biopsy aspiration and cytological exam.

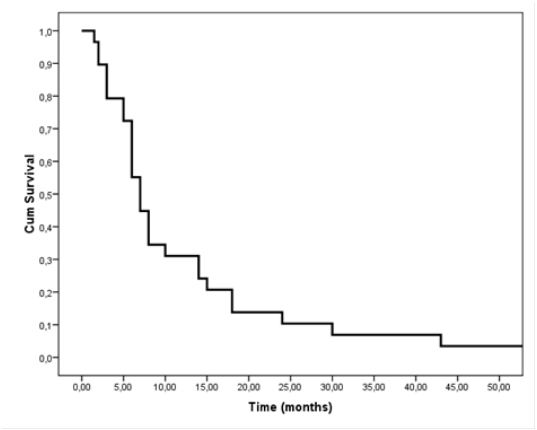

Figure 1.
The Kaplan-Meier curve for the thyroid dysfunction-free survival in patients treated with sunitinib

Thyrotoxicosis was diagnosed in 4 patients (13.8%), 2 M/2 F, aged 56.75 ± 12.5 years. Median duration of TKI treatment till diagnosis of thyrotoxicosis tends to be shorter (6.5 months, 25th percentile: 5.75 months, 75th percentile: 7.25 months, range 5 - 8 months) than in sunitinib-induced hypothyroidism, but the difference was not statistically significant (Figure 2). Median TSH at diagnosis was 0.04 mIU/L (25th percentile: 0.025 mIU/L, 75th percentile: 0.06 mIU/L, range 0.01 - 0.1). Overt thyrotoxicosis was diagnosed in 2 patients and subclinical thyrotoxicosis in 2 patients. Thyrotoxicosis was transient in all patients, followed by persistent hypothyroidism. Overall, all patients included in this study developed hypothyroidism; thyrotoxicosis preceded hypothyroidism in 4 out of 29 patients (13.8%).

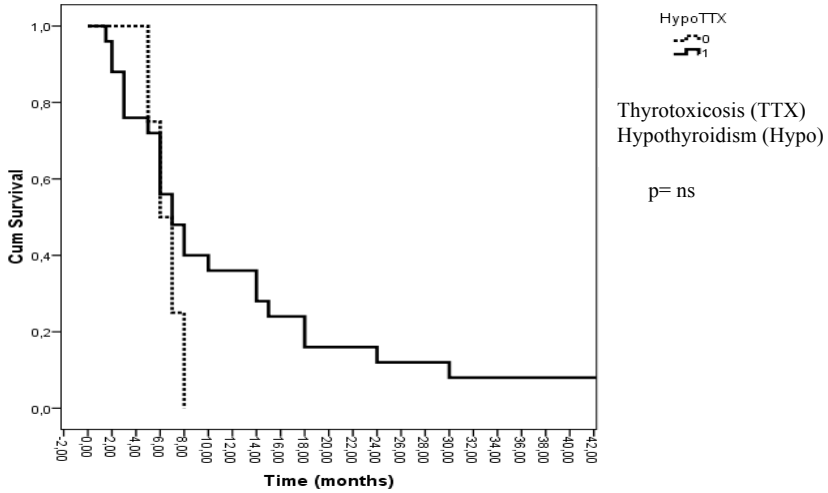

Figure 2.
The Kaplan-Meier curve for hypothyroidism (continuous line) and thyrotoxicosis (dotted line) - free survival in patients treated with sunitinib

Recurrent episodes of transient destructive thyrotoxicosis, proved by reduced ^{131}I radioiodine uptake at both 2 and 24 hours and markedly increased serum thyroglobulin levels (300 ng/mL) were noticed in one patient; between thyrotoxicosis episodes there was an episode of subclinical hypothyroidism and finally the patient developed

persistent overt hypothyroidism requiring levothyroxine therapy.

In our series, we reported only patients with sunitinib-induced thyroid dysfunction.

All the patients were euthyroid before starting treatment with sunitinib. Three patients (10.3%) had type 2 diabetes mellitus (one requiring insulin treatment and two on oral antidiabetic agents, but diabetes is an independent predictor of disease progression, all-cause mortality and cancer-specific mortality in RCC [13, 30]. In the literature, sunitinib-induced hypothyroidism occurred with frequency varying between 14 - 85% [8].

Median duration of sunitinib treatment till diagnosis of thyroid dysfunction was 7 months in our series, without significant differences between median time to diagnosis of hypothyroidism (7 months) and thyrotoxicosis (6.5 months), respectively. In a series of 81 patients with mRCC, hypothyroidism occurred in 37% of patients, within a median of 3 months (range: 1 - 18) [9]. In another series of 31 patients treated with sunitinib, 52% of patients developed hypothyroidism within 3 months [45]. This difference could be explained by repeated TSH and FT_4 in day 1 of each 6-week sunitinib cycle. Therefore, it is strongly recommended to measure TSH and FT_4 at each treatment cycle for a precocious diagnosis of sunitinib-induced thyroid dysfunction.

Later diagnosis of hypothyroidism in our series was associated with a predominance of overt hypothyroidism (17 out of 25 patients) over subclinical hypothyroidism (8 out 25 patients). The risk of developing hypothyroidism increased with time and number of cycles of sunitinib therapy as shown by Dessai *et al* who found in a series of 42 patients mildly elevated TSH (5 - 7 mIU/L) in 17% of cases, moderately elevated TSH (7 - 20 mIU/L) in 14% of cases and markedly elevated TSH (> 20%) in 21% of cases [17]. In our study one patient with sunitinib-induced hypothyroidism associated a diffuse sclerosing variant of papillary thyroid carcinoma, responsive to radioiodine treatment; in the literature, a positive correlation has been found between the expression of VEGF and a more aggressive phenotype of differentiated thyroid cancer [1, 7]. Sunitinib and sorafenib are already used for treatment of progressive, radioactive iodine-resistant differentiated thyroid cancer [11].

In our study, the majority of patients showed thyroid gland atrophy. A volumetric analysis of thyroid performed by computed tomography revealed statistically significant atrophy of the thyroid (mean atrophic ratio = 0.58 for thyroid, as compared with 0.74 for pancreas and 0.82 for spleen) [47]. Pani *et al* reported thyroid volume decreased in 24/27 patients (89%), with a higher reduction in TPO antibodies positive patients [36].

Sunitinib-induced thyrotoxicosis was reported rarely compared with hypothyroidism. Dessai *et al* reported a prevalence of thyrotoxicosis (isolated TSH suppression) of 10% [17]. In our case, thyrotoxicosis preceded hypothyroidism in 4 out of 29 cases (13.8%) and one patient showed recurrent episodes of transient thyrotoxicosis followed by persistent hypothyroidism. Grossman *et al.* reported a series of 6 cases, 2 with severe and 4 mild, self-limited forms of thyrotoxicosis; the last one finally progressed to hypothyroidism, after recurrent episodes of thyrotoxicosis [24]. The mechanism of transient thyrotoxicosis in our case was destructive thyroiditis, proved by high thyroglobulin levels and significantly reduced radioiodine uptake. Similar pattern of thyrotoxicosis was reported by Sato *et al*, during the second and third treatment cycles [42]. Overall, between 3.2 - 40% of patients showed suppressed TSH due to destructive thyroiditis prior to hypothyroidism [21, 38, 41].

Median duration from the diagnosis of renal cell carcinoma to the diagnosis of thyroid dysfunction was 9 years the in studied patients, due to distance from diagnosis to the beginning of therapy with TKI, but in urological cancers it is very important to have an early diagnosis [22] and treatment. Several studies showed that TKI side-effects (hypertension, hypothyroidism and hand-foot syndrome) are potential biomarkers of treatment efficacy [8]. Sunitinib-induced hypothyroidism may be a predictive clinical marker for better survival in patients with mRCC [6, 33] as it was reported to be associated with longer progression free survival and in some series with longer overall survival [40, 44].

Bozkurt *et al* reported a higher rate of objective remission (46.7% *vs*. 13.7%, p = 0.001), a higher median progression-free survival (17 months *vs.* 10 months, p = 0.001) and a higher overall survival (35% *vs.* 20%, p = 0.019) in patients with sunitinib-induced hypothyroidism *vs.* euthyroid patients [9]. Longer progression free survival was also reported in hypothyroid patients by other authors: 25.3 *vs.* 9 months [29], 12.2 *vs*. 9.4 months [45] and 28.3 months *vs*. 9.8 months [10]. However, there were discordant data concerning overall survival (OS): some studies found an increased OS [9, 45], while other found no differences in OS [29].

Follow-up of thyroid function tests in patients treated with TKIs is mandatory [25]. Recently, a thyroid function monitoring algorithm in sunitinib-treated patients was proposed: TSH measurement is recommended at day 28^{th} of each 6-week treatment cycle; if an increased TSH is found, TSH has to be repeated at the end of OFF period; persistent increased TSH leads to the measurement of FT_4 and initiation of levothyroxine treatment, individualized depending on patients' symptoms and thyroid stimulating hormone level, and nevertheless the

renal function and inflammatory state [35]. In case of daily administration regimen, TSH should be measured monthly [25].

Conclusions

Close monitoring of thyroid function is recommended in sunitinib-treated patients, irrespective of treatment duration. Persistent hypothyroidism requires levothyroxine treatment. Thyrotoxicosis may occur, due to destructive thyroiditis and do not need antithyroid treatment, as it is frequently followed by hypothyroidism.

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