Sorafenib therapy decreases the clearance of thyrotropin

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Abstract
Objective: Thyroid function abnormalities are common during treatment with tyrosine kinase inhibitors such as sorafenib. Suggested causes are direct effects on thyroid tissue and increased extrathyroidal metabolism of serum thyroxine and 3,5,3-triiodothyronine. We postulated that tyrosine kinase inhibitors may affect the peripheral metabolism of TSH as well. The effect of sorafenib on TSH clearance was studied.
Design: In a study of athyreotic patients on TSH suppression therapy, TSH concentrations were measured after recombinant human TSH (rhTSH) injections before and after 26 weeks of sorafenib therapy.
Methods: Before and after the last week of sorafenib therapy, 20 patients with progressive differentiated thyroid carcinoma received a standard dose regimen of two injections 0.9 mg rhTSH on two consecutive days. TSH concentrations were measured 48 h (TSH48 h) and 96 h (TSH96 h) after the first rhTSH injection. The area under the curve (TSH-AUC), reflecting TSH content between 48 and 96 h following rhTSH administration, was calculated.
Results: TSH48 h levels (120.5 mU/l before vs 146.3 mU/l after; \( P \approx 0.029 \)), TSH96 h levels (22.0 mU/l before vs 35.5 mU/l after; \( P < 0.001 \)), and TSH-AUC (142.7 vs 186.8 mU/l; \( P < 0.001 \)) were significantly higher after sorafenib treatment. Higher sorafenib doses were associated with increased changes in TSH96 h and TSH-AUC. In two patients, TSH levels after sorafenib therapy exceeded 200 mU/l.
Conclusions: Sorafenib therapy is accompanied by higher rhTSH levels, probably due to a decreased TSH clearance. Further studies are recommended to clarify whether a decreased clearance of TSH is sorafenib specific.

Introduction
Sorafenib is a tyrosine kinase inhibitor approved for treatment of metastatic renal cell carcinoma and irresectable hepatocellular carcinoma (1). As phase II trials demonstrated promising effects of sorafenib on tumor progression in patients with locally advanced or metastatic radiiodine-refractory thyroid carcinoma, a phase III trial has started to evaluate the safety and efficacy of sorafenib for these indications (2). In vitro studies showed that sorafenib could inhibit tumor growth in several other malignancies (3).

The increasing use of targeted therapies such as sorafenib warrants a critical evaluation of potential adverse effects of these drugs. Tyrosine kinase inhibitors are well known for their impact on the pituitary–thyroid axis (4). Thyroid function abnormalities, particularly TSH elevations, are common during treatment with sorafenib, occurring in 10–68% of sorafenib-treated patients (1, 5). Direct effects on the thyroid, such as destructive thyroiditis, may play a role (5). In a previous study, we reported that sorafenib could also enhance peripheral thyroxine (T4) and 3,5,3-triiodothyronine (T3) metabolism, irrespective of a direct effect on the thyroid gland (6).

However, the origin of sorafenib-induced TSH elevations in thyroidectomized patients has not been extensively studied. By design, we had the opportunity to study the effect of sorafenib on metabolic clearance of TSH. In a study of athyreotic patients on TSH suppression therapy for advanced thyroid carcinoma, TSH concentrations after recombinant human TSH (rhTSH) injections were measured before and directly after 26 weeks of sorafenib therapy. As the rhTSH doses were identical at these two occasions and pituitary TSH secretion was continuously inhibited due to TSH suppression therapy, differences in TSH levels might point toward an independent effect of sorafenib on TSH clearance. Therefore, this study aimed to determine whether sorafenib could impact on TSH metabolism.
Materials and methods

Study design

The effect of sorafenib on TSH clearance was analyzed in athyreotic patients under TSH suppressive therapy (Fig. 1). All patients had undergone total thyroidectomy followed by radioiodine ablative therapy. Sorafenib was administered within the framework of an open, single-center, single-arm, 26-week phase II study, which intended to achieve reinduction of radioiodine uptake in patients with radioiodine-refractory progressive metastatic or locally advanced differentiated thyroid carcinoma (7). Sorafenib was started at a dose of 400 mg orally twice a day. Doses were lowered in case of side effects. Exclusion criteria were pregnancy, contraindications for rhTSH administration, and contraindications for sorafenib. The institutional review board approved the study and all patients provided written informed consent before participation.

At baseline and after 26 weeks of sorafenib therapy, patients received a standard dose regimen of two injections 0.9 mg rhTSH (Thyrogen, Genzyme, Naarden, The Netherlands) on two consecutive days. Fasting blood samples were taken for TSH and thyroglobulin measurements 48 and 96 h after the first rhTSH injection.

Patients visited the hospital every 4 weeks for the assessment of thyroid function and biochemical safety parameters, a physical examination and supervision on compliance with study medication. Body weight was measured every month and length at baseline. All patients were treated with levothyroxine (L-T4), which was aimed to maintain a TSH concentration <0.1 mU/l.

Study parameters

TSH concentrations were measured 48 h (TSH 48 h) and 96 h (TSH 96 h) after the first rhTSH injection. At these occasions, free T4 (FT4), total T4, free T3, total T3, and reverse T3 were also measured. The effect of rhTSH stimulus on serum TSH concentration was also computed by a time-average (TSH area under the curve (TSH-AUC)) analysis (8). TSH-AUC (mU/L×2 days) reflects the total TSH content between 48 and 96 h following the first rhTSH injection and was calculated by a simple trapezoidal method (9). Weight, BMI, and body surface area (BSA) were calculated before and after sorafenib treatment. BSA (m²) was determined by Dubois-Dubois formula (10). Glomerular filtration rate (GFR) was calculated according to Cockcroft and Gault’s formula. Mean sorafenib dose (MSD; defined as the mean dose of sorafenib (mg) received during 26 weeks uncorrected for weight) was calculated to study a potential dose–response effect of sorafenib on TSH. ∆Weight, ∆BMI, ∆BSA ∆GFR, ∆ basal TSH, ∆TSH 48 h, ∆TSH 96 h, and ∆TSH-AUC were calculated by subtracting the levels before treatment from those after 26 weeks of treatment.

Assays

TSH was measured by a chemiluminescence assay (Vitros ECI Immunodiagnostic System Ortho-Clinical Diagnostics via GE Healthcare, Rochester, NY, USA). The detection limit was 0.005 mU/l (intra-assay coefficient, 4%).

Statistical analysis

Data are reported as mean ± S.D., median (range), or proportions. The effect of sorafenib was analyzed by the t-test for paired data, comparing measurements between baseline and after 26 weeks of sorafenib therapy. To evaluate whether changes in TSH parameters after rhTSH administration between baseline and after 26 weeks of sorafenib therapy (∆TSH 48 h, ∆TSH 96 h, and ∆TSH-AUC) were related to changes in basal TSH, anthropometric variables (∆weight, ∆BMI, and ∆BSA) and MSD, univariate, and multivariate regression analyses were performed. TSH parameters were log-transformed when required. Differences were considered statistically significant at P<0.05. All calculations were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Patients

Between October 2007 and October 2008, 32 patients were included. In total, 22 patients completed 26 weeks of treatment with sorafenib; one patient did not start therapy and nine patients discontinued treatment for reasons described previously (6). Pretreatment rhTSH injections were not administrated in two patients for clinical reasons. Posttreatment rhTSH concentrations were not measured in an additional three patients. Therefore, in 20 patients, the effect of 26 weeks of sorafenib on TSH 48 h concentrations could be analyzed, and in 17 of these patients, the effect of 26 weeks of
sorafenib on TSH$_{96}$ concentrations could be analyzed. The median age of the cohort was 64 years (range, 53–82 years), and 14 (70%) were male. One patient had locally advanced disease only and the remaining 19 patients had distant metastases. Mean BMI at baseline was 25.6 ± 3.5. In all patients, a TSH level below 0.1 mU/l was pursued (median, 0.02; range, 0.005–0.33). In 14 patients (70%), sorafenib doses were lowered during the study period. The efficacy of sorafenib with respect to tumor progression and the presence of adverse effects have been described previously (7).

**TSH-related parameters**

rhTSH was administered at baseline and after 26 weeks of sorafenib therapy. TSH$_{48}$ h levels (120.5 ± 24.2 mU/l before vs 146.3 ± 56.2 mU/l after; $P = 0.029$) and TSH$_{96}$ h levels (22.0 ± 11.0 mU/l before vs 35.5 ± 18.6 mU/l after; $P = 0.001$) were clearly higher after treatment. In accordance, TSH-AUC was also higher after sorafenib therapy (142.7 ± 32.6 vs 186.8 ± 76.4 mU/l; $P = 0.001$). Thirteen of 20 patients (65%) had higher TSH$_{48}$ h concentrations following sorafenib. TSH$_{48}$ h concentration increased to levels above 200 mU/l under sorafenib treatment in two patients (212.3 and 340.3 mU/l respectively). Sixteen of 17 patients (94.1%) had an increase in TSH$_{96}$ h and TSH-AUC levels before and under sorafenib are shown in Fig. 2.

**Anthropometric parameters and GFR**

Patients showed a considerable decline in body weight (76.3 ± 12.7 before vs 69.3 ± 13.2 after treatment; $P \leq 0.001$) as well as in BMI (25.6 ± 3.5 before vs 23.1 ± 4.0 after; $P \leq 0.001$). In accordance with these observations, BSA diminished significantly (1.9 ± 0.2 before vs 1.8 ± 0.2 after; $P \leq 0.001$). GFR was similar before and after treatment (83.4 ± 14.3 before vs 82.7 ± 16.8 after; $P = 0.813$).

**Dose–response effect**

Regression analysis showed that TSH levels before and after treatment were not related to basal TSH, body weight, BMI, or BSA. GFR was related to TSH levels after treatment (TSH-AUC: $B = -0.033; P = 0.01$). No associations were found between ΔTSH$_{48}$ h and Δbasal TSH ($B = 0.005; P = 0.87$), Δweight ($B \leq 0.001; P = 0.99$), ΔBMI ($B = -0.010; P = 0.82$), ΔBSA ($B = -0.069; P = 0.96$), or ΔGFR ($B = -0.002; P = 0.76$). Similarly, ΔTSH$_{96}$ h was not related to Δbasal TSH ($B = 0.041; P = 0.42$), Δweight ($B = -0.019; P = 0.42$), ΔBMI ($B = -0.072; P = 0.33$), ΔBSA ($B = -2.154; P = 0.29$), or ΔGFR ($B = -0.016; P = 0.22$). MSD was associated with ΔTSH$_{96}$ h ($B = 0.002; P = 0.02$) and ΔTSH-AUC ($B = 0.003; P = 0.03$), indicating that higher sorafenib doses were associated with increased changes in TSH parameters. Multivariate analysis including Δ basal TSH, Δweight, ΔBMI, ΔBSA, and ΔGFR as covariates did not materially change these results.

**Discussion**

The present paper studied whether the tyrosine kinase inhibitor sorafenib could affect the peripheral clearance of TSH. Patients injected with identical doses of rhTSH before and after treatment had significantly higher TSH concentrations after 26 weeks of sorafenib therapy. Higher
sorafenib doses were associated with increased changes in TSH parameters, indicating a dose–response effect.

How can we explain our findings? An effect of sorafenib on pituitary TSH secretion is unlikely, as the increase in basal TSH concentration after sorafenib was only marginal and not sufficient to explain the increased TSH levels after rhTSH. Anthropometric variables such as body weight, BMI, and BSA have been associated with serum TSH levels after rhTSH administration in two independently conducted studies (8, 11). It was therefore also investigated to which extent changes in anthropometric variables may contribute to variation in TSH concentrations following rhTSH administration. However, anthropometric variables were not related to TSH parameters in our regression model. These findings are in line with a large study conducted on 311 patients treated for differentiated thyroid carcinoma in which no correlation between BMI, BSA, and TSH concentrations was found (12). Because only minimal changes in renal function were observed, an excretion defect of TSH is unlikely. Our findings are most likely explained by an effect of sorafenib on metabolic clearance of TSH. Although direct effects of medication on TSH secretion have been reported (13), clinical or basic research evaluating the impact of drugs on TSH metabolism is scarce. The specific glycosylation pattern of TSH carbohydrate structures is a major determinant of its renal and hepatic metabolism, with increased sialylation associated with prolonged plasma half-life (14). Hypothyroidism was associated with increased sialylated pituitary TSH isoforms in the mammalian, including human circulation (15, 16). Evidence supports the notion that slower TSH degradation could, at least partly, explain supranormal TSH levels in hypothyroid states (14, 17). One could speculate that sorafenib-induced hypothyroidism may be accompanied by changes in TSH carbohydrate structures, i.e. an increased sialylation, promoting a slower metabolic clearance rate. However, a similar mechanism for processing of exogenous TSH is unlikely. Sorafenib is a potent inhibitor of several tyrosine kinases (3).

As tyrosine kinases play an important role in receptor-mediated endocytosis of glycoproteins (18), a direct effect of sorafenib on hepatic receptors dependent on kinase activity may be plausible. Indeed, an in vitro study showed that tyrosine kinase inhibitors could interfere with endocytosis of the hepatic asialoglycoprotein receptor, one of the major receptors involved in clearance of glycoproteins such as TSH (14, 19).

Two patients had inappropriately high TSH levels (> 200 mU/l) after sorafenib. In radioiodine-treated metastatic thyroid carcinoma patients, rhTSH stimulation is used off-label as a beneficial alternative to escape the negative effects of thyroid hormone withdrawal (20). Although rhTSH administration could be regarded a safe and well-tolerated diagnostic and therapeutic option in the majority of patients treated for thyroid carcinoma, in patients with advanced disease, TSH concentrations exceeding 200 mU/l may cause serious complications such as violent bone pain, nonresponsive severe headache, local edema, and focal hemorrhage due to swelling at the location of metastases (11). Sarcopenic patients might be more prone to sorafenib-induced toxic TSH levels, as sorafenib concentrations and dose-limiting toxicities are known to be higher in this subgroup (21).

In conclusion, this study showed that tyrosine kinase inhibitors could affect TSH levels via extrathyroidal mechanisms, as demonstrated by a diminished clearance of rhTSH after sorafenib. Combined measurement of TSH and FT4 could be the most appropriate way to evaluate thyroid function in patients treated with sorafenib, as TSH concentrations may be possibly affected by processes independent of the negative feedback of peripheral thyroid hormone concentration.

Of note, other forms of (drug-induced) thyroid dysfunction may be accompanied by an effect on TSH metabolism as well. More research is warranted to evalate whether tyrosine kinase inhibitors could also affect the clearance of other exogenously administered glycoproteins.

Declaration of interest

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