Differentiated thyroid carcinoma : treatment and clinical consequences of therapy

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Sorafenib induced hypothyroidism is associated with increased type 3 deiodination

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Abstract

Background

Therapy with tyrosine kinase inhibitors is associated with thyroid dysfunction. Decreased serum thyroid hormone levels during tyrosine kinase inhibitors are also observed in athyreotic patients with thyroid carcinoma. We therefore hypothesized that tyrosine kinase inhibitors may influence thyroid hormone metabolism.

Aim

The aim was to study the effects of sorafenib therapy on serum thyroid hormone concentrations and iodothyronine deiodination in athyreotic patients.

Design

The design included a prospective open, single-center, single-arm 26-wk study.

Methods

We measured serum thyroxine (T4), free T4, 3,5,3-triiodothyronine (T3), free T3, reverse T3 (rT3), and TSH concentrations at baseline and after 26 wk in 21 patients with progressive non-medullary thyroid carcinoma treated with sorafenib. Ratios of T3/T4 and T3/rT3, which are independent of substrate availability and reflect iodothyronine deiodination, were calculated.

Results

Serum free T4 and T3 levels, adjusted for levothyroxine dose per kilogram body weight, decreased by 11 and 18%, respectively, whereas TSH levels increased. The serum T3/T4 and T3/rT3 ratios decreased by 18 and 22%, respectively, which is compatible with increased type 3 deiodination.

Conclusions

Sorafenib enhances T4 and T3 metabolism, which is probably caused by increased type 3 deiodination.

Introduction

Therapy with tyrosine kinase inhibitors in patients with malignancies is associated with alterations in thyroid hormone parameters. Sunitinib has been associated with hypothyroidism in 14–85% of the patients, ranging from transient increases in TSH to persistent hypothyroidism, requiring thyroxine substitution (1–6). In some patients, sunitinib induced hyperthyroidism as well (7–9). Both sunitinib induced hypothyroidism and hyperthyroidism may be caused by destructive thyroiditis, but other mechanisms, such as interference of sunitinib with thyroid peroxidase (4) or inhibition of thyroidal vascularization leading to thyroid atrophy (10, 11), have been proposed. Likewise, sorafenib was associated with TSH elevations in 18% of patients with metastatic renal cell carcinoma (12). All of the above mentioned studies were performed in patients with intact thyroid glands. However, thyroid function abnormalities have also been observed during therapy with imatinib (13, 14), motesanib (15), and sorafenib (16) in athyreotic patients with medullary thyroid carcinoma and non-medullary thyroid carcinoma. Imatinib increased TSH levels in all patients with medullary thyroid carcinoma (13, 14). Therapy with motesanib caused TSH elevations in 22% of 93 patients with non-medullary thyroid carcinoma. Sorafenib was associated with increased TSH levels in 33% of thyroid carcinoma patients (16). Because an increased need of thyroxine is observed in athyreotic patients who are treated with tyrosine kinase inhibitors, the mechanisms of hypothyroidism may include alterations in thyroid hormone metabolism. Stepwise deiodination is the major route of thyroid hormone degradation and is mediated by iodothyronine deiodinases (D1, D2, and D3) (17) and by hepatic conjugating enzymes (18). No human studies have been published to address the effect of sorafenib on peripheral thyroid hormone metabolism. We therefore studied the effects of sorafenib, administered for 26 weeks, on peripheral thyroid hormone metabolism in athyreotic humans.

Patients and Methods

Design

The effects of sorafenib on peripheral thyroid hormone metabolism were analysed in an open, single center, single arm 26-week prospective phase II study, intended to achieve reinduction of RaI uptake in athyreotic patients with progressive metastatic or locally advanced non-medullary thyroid carcinoma. Results of this study have been published recently (19). Sorafenib was initially administered at a dose of 400 mg orally twice daily. Exclusion criteria were pregnancy, contraindications for the application of recombinant human TSH (rhTSH), and contraindications for the use of

sorafenib. The institutional review board approved the study and all patients provided written informed consent.

Before initiation of sorafenib therapy and at 26 weeks, the patients underwent computed tomography scans for analysis of tumor dimensions and rhTSH (Thyrogen®, Genzyme, Naarden, The Netherlands) assisted 4 mCi diagnostic scintigraphies. During the study patients visited the hospital every month for assessment of thyroid function parameters, biochemical safety parameters and a physical examination. Fasting morning blood samples were stored at -80°C until analysis. All patients were treated with levothyroxine, which was adjusted if needed to maintain a target TSH concentration below 0.1 mU/L. Only patients who completed 26 weeks of treatment with sorafenib were included in the present analysis (per protocol analysis).

Study aims

The objective of this study was to evaluate the effects of sorafenib on thyroid hormone serum levels and to evaluate the effects of sorafenib on iodothyronine deiodinase activity.

Study parameters

The following thyroid function parameters were measured: serum TSH, free thyroxine (FT4), total thyroxine (T4), free 3,5,3- triiodothyronine (FT3), total 3,5,3-triiodothyronine (T3), and reverse 3,5,3-triiodothyronine (rT3). Because levothyroxine dosages were adjusted during the study according to serum TSH levels, serum thyroid hormone levels were corrected for the daily levothyroxine dose and body weight. Dose-adjusted FT4 was calculated as follows: (FT4 (pmol/liter) * weight (kg))/levothyroxine dose (µg).

To assess effects of sorafenib on iodothyronine deiodination, ratios of serum levels of T3/T4 and T3/rT3 were calculated. The T3/rT3 ratio is considered to be a sensitive indicator of the peripheral metabolism of thyroid hormone, being positively influenced by D1 and D2 deiodinase and negatively by D3 deiodinase. Serum thyroxine-binding globulin (TBG) levels and FT4/T4 and FT3/T3 ratios were calculated to exclude effects of sorafenib on thyroid hormone binding proteins.

Assays

Fasting blood samples were collected before daily levothyroxine ingestion at both baseline and 26 wk and stored at -80°C. TSH, FT4, T4, T3, and TBG were measured by chemiluminescence assays (Vitros ECI Immunodiagnostic System; Ortho-Clinical Diagnostics via GE Healthcare, Rochester, NY). FT3 was measured with a RIA (Trinity

Biotech, Bray, Ireland). rT3 was measured with an in-house RIA (20). The detection limit of the TSH assay was 0.005 mU/liter. Within-assay coefficients of variation amounted to 4% for TSH, 2% for T4, 2% for T3, and 3–4% for rT3.

Statistics

Data are reported as mean ± SD, median (range) or proportions. Differences in thyroid hormone parameters were analyzed using the two tailed Student's t-test for paired data, comparing measurements between baseline and after 26 weeks sorafenib therapy for normally distributed data or with a Wilcoxon test for non-normally distributed data. Differences were considered statistically significant at $P < 0.05$. All calculations were performed using SPSS 16.0 for windows (SPSS, Chicago, IL)

Results

Between October 2007 and October 2008, a total of 32 patients were included in the study. Twenty-two patients completed the 26 weeks because one patient chose not to start therapy and nine patients discontinued treatment during the 26 wk for disease progression (four patients), adverse events (four patients), and the patient's request (one patient) as reported previously (19). Because the thyroid hormone profile of one patient was not recorded, 21 patients were included in the present analysis: seven females, 14 males, with a median age of 65 yr (range, 53–82 yr), all with distant metastases of nonmedullary thyroid carcinoma (local, 4%; lungs only, 29%; lungs and bones, 24%; lungs and local, 14%; other, 29%). The efficacy of sorafenib with respect to tumor progression and the presence of adverse effects has been reported previously (19). Effects of sorafenib on study parameters are given in **Table 1**.

We observed a profound decrease in mean body weight of 6 kg. During the study, the levothyroxine dose per kilogram body weight was significantly increased (2.48 μg/kg before *vs.* 2.71 μg /kg after sorafenib; P=0.008) **(Table 1, Figure 1**). Nevertheless, TSH increased significantly from 0.051 to 0.545 mU/liter (P=0.023). Despite the increase in thyroxine dose, significant decreases in serum T3 (1.90 *vs.* 1.60 nmol/liter) and dose-adjusted free T3 levels (1.59 *vs.* 1.35 pmol*kg/μg) were observed. Absolute rT3 levels tended to increase after sorafenib therapy, and T3/T4, T3/rT3, and T4/rT3 ratios decreased significantly by 18, 22, and 7%, respectively, reflecting an increased conversion of T4 into rT3. Potential effects of sorafenib on thyroid hormone binding proteins were assessed by measuring TBG levels, which were not influenced by sorafenib, and by calculating ratios of free over total T4 and T3 concentrations, which did not differ before and after sorafenib.

Table 1: Thyroid hormone parameters

	N	Baseline	26-weeks sorafenib	P –value
Weight (kg)	21	77.3 ± 13.5	71.0 ± 14.2	<0.001
Sorafenib dose (mg/kg/day)	21	10.4 ± 2.4	8.4 ± 2.7	0.003
Levothyroxine dose (µg/kg/day)	21	2.48 ± 0.67	2.71 ± 0.61	0.008
T4 (nmol/L)	21	149.4 ± 31.9	152.9 ± 37.7	0.664
T3 (nmol/L)	20	1.90 ± 0.33	1.60 ± 0.34	0.007
FT4 (pmol/L)	21	27.3 ± 5.9	26.6 ± 6.9	0.587
FT4 (pmol/L)***weight** (kg) / levothyroxine dose (µg)	21	11.7 ± 3.6	10.4 ± 3.6	0.034
FT3 (pmol/L)	13	5.43 ± 0.71	4.80 ± 1.09	0.075
FT3 (pmol/L)***weight** (kg) / levothyroxine dose (µg)	13	1.59 ± 1.38	1.35 ± 1.15	0.005
rT3 (nmol/L)	20	0.68 (0.50-1.02)	0.79 (0.63-1.12)	0.091 *
TSH (mU/L)	21	0.01 (0.005-0.33)	0.100 (0.005-4.670)	0.023 *
TBG (mg/L)	21	19.8 ± 4.3	19.5 ± 4.0	0.620
FT3/T3 * 10^3	13	2.73 ± 0.33	2.93 ± 0.31	0.279
FT4/T4 * 10^3	21	5.55 ± 0.94	5.84 ± 0.95	0.124
T3/T4 * 100	20	1.28 ± 0.00	1.05 ± 0.00	<0.001
T3/rT3	20	2.74 ± 0.50	2.16 ± 0.53	<0.001
T4/rT3	20	220 ± 27	205 ± 32	0.036

Data expressed as mean ± SD or median (range)
* Wilcoxon -test

Discussion

In this study, we assessed the relationship between treatment with the multiple target kinase inhibitor sorafenib and alterations in thyroid hormone parameters. Therapy with tyrosine kinase inhibitors is associated with hypothyroidism. Proposed mechanisms include direct effects of these drugs on the thyroid, including destructive thyroiditis (4,10,11). Because thyroid function abnormalities have also been observed in athyreotic patients on thyroxine substitution, the mechanisms of hypothyroidism may include alterations in thyroid hormone metabolism as well. We hypothesized that sorafenib may influence the activities of iodothyronine deiodinases (D1, D2, and D3) (17), which has not been studied in humans so far. We found that a higher substitution dose of thyroxine was needed to maintain serum FT4 levels. These findings are consistent with a previous report in which eight imatinib treated patients that had undergone thyroidectomy required substantial increases in levothyroxine replacement dose (13). Indeed, the increased need of levothyroxine may be underestimated because some patients may have been overtreated before initiation of the trial. In addition, we found a clear decrease in serum T3/T4, T3/rT3, and T4/rT3 ratios. These

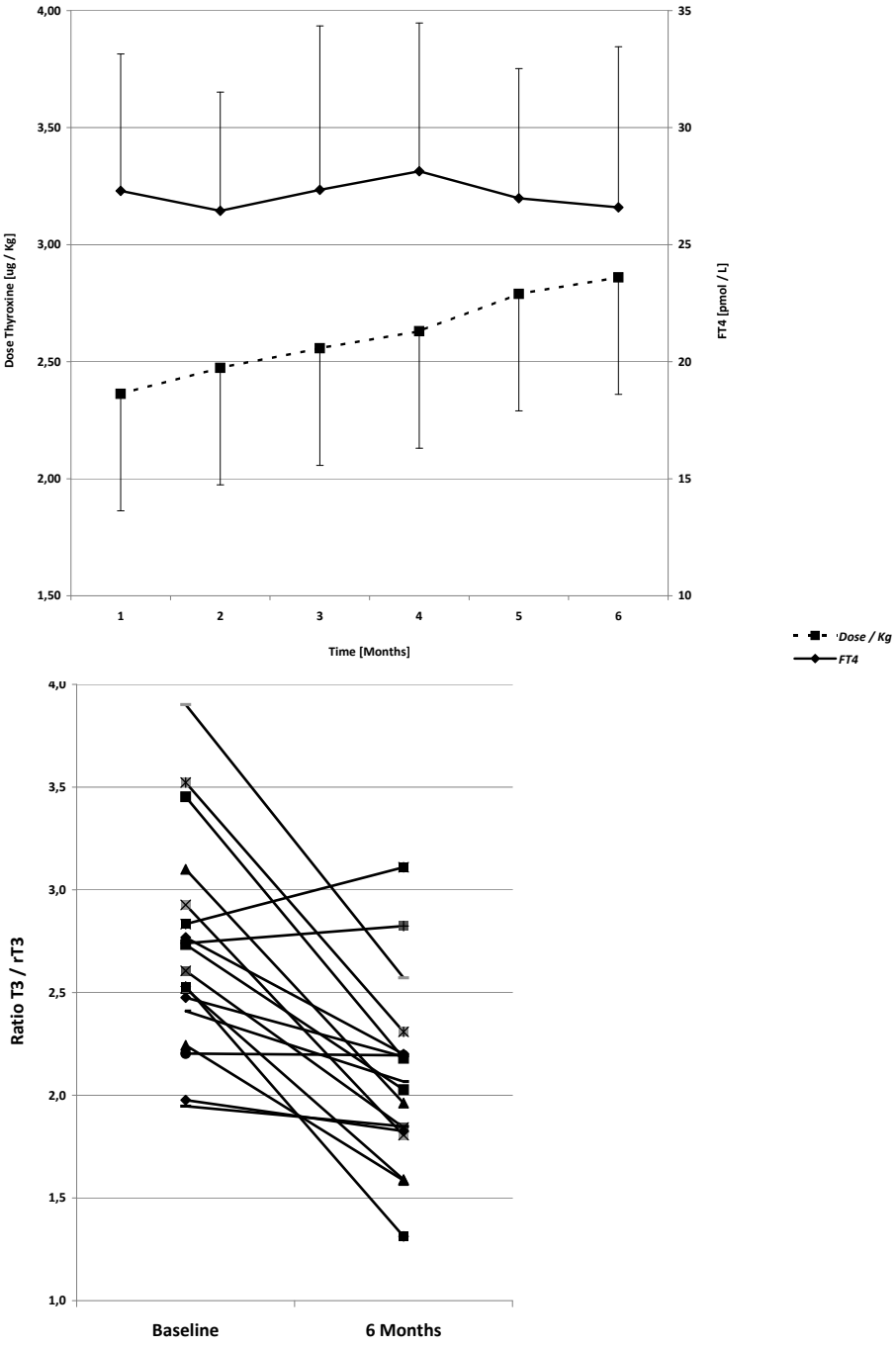

Figure 1

(A) Relation between levothyroxine dose adjusted for body weight (Dose Thyroxine) and serum FT4 concentrations during 6 months of treatment with sorafenib. (B) Individual T3/rT3 ratios before and 6 months after treatment with sorafenib.

ratios reflect alterations in the peripheral metabolism of thyroid hormone, being positively influenced by deiodinases D1 and D2 and negatively by D3 (17). Moreover, they are independent of levothyroxine administration. The decreased T3/T4 and T3/rT3 ratios may be caused by a decrease in D1 and/or D2 activity. However, this would be associated with a decreased rather than an increased T4 metabolism. Therefore, the decreased T3/T4 and T3/rT3 ratios are best explained by an increased D3 activity. The fact that, 2 months after the start of sorafenib, a significantly higher T4 dose per kilogram body weight was necessary to maintain FT4 concentrations strongly suggests that the phenomenon is already present early after initiation of sorafenib therapy. It is worthwhile to further elucidate the effects of sorafenib on D3 in *in-vitro* studies. It is unlikely that the increased D3 activity reflects a state of non thyroidal illness because serum TSH increased during sorafenib, whereas in non thyroidal illness, decreased rather than increased TSH levels would be expected. Although it can be hypothesized that decreased absorption of T4 could also have played a role, the interval between sorafenib and thyroxine intake was approximately 12 h. In addition, decreased T4 absorption would not affect T3/T4 and T3/rT3 ratios. No changes in TBG levels and the ratios between free and bound thyroid hormones were observed, ruling out effects of sorafenib on thyroid hormone binding proteins, which again, even if present, would not have affected the T3/rT3 ratio. It may hypothesized that sorafenib may also influence conjugation of thyroid hormone with glucuronates and sulfates by hepatic microsomal enzymes. However, altered conjugation would not influence T3/rT3 ratios. The fact that the increase in overall rT3 levels was non significant may suggest that rT3 degradation may be enhanced as well. It is likely that, because rT3 is the preferred substrate for type 1 deiodinase (in the absence of hyperthyroidism), increased rT3 may lead to enhanced type 1 deiodinase-mediated rT3 degradation.

In conclusion, this study shows that, in addition to direct effects of tyrosine kinase inhibitors on the thyroid gland, enhanced peripheral metabolism of thyroid hormone, likely by activity of type 3 deiodinase, may contribute to hypothyroidism during therapy with these drugs.

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