LETTER TO EDITOR

Lack of imatinib-induced thyroid dysfunction in a cohort of non-thyroidectomized patients

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To the Editor

Understanding the role of tyrosine kinase (TK) proteins in the pathogenesis of various tumors triggered the development of drugs that specifically block TK actions (1). Imatinib, one of the drugs in that class, has favorably altered the natural history of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (1). However, given the short experience with these drugs, the full spectrum of adverse effects remains unknown. Cardiotoxicity (2) and bone metabolism alterations (3) have been reported in association with TK inhibitor therapy. Recently, high rates of hypothyroidism have been described in patients receiving sunitinib (4, 5). In addition, adjustment of thyroid hormone replacement in thyroidectomized patients under sunitinib or imatinib therapy, with the need of up to 350% increase in levothyroxine dose, has also been reported (6). Due to similar mechanisms, it is possible that imatinib is also associated with thyroid dysfunction in non-thyroidectomized patients. Because of the widespread use of this drug, we sought to evaluate the impact of imatinib therapy on thyroid function.

Patients with CML under imatinib therapy, followed at the Hematological Division of Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil), between March and October 2007, were eligible for the study. Patients who used drugs with potential interference in thyroid function tests 6 months prior to the study entry or with known previous thyroid dysfunction were excluded. All measurements were performed using ECLIA (Roche). Interassay coefficients of variation were as follows: thyrotrophin (TSH), 1.6%; thyroxine (T₄), 3.5%; (free T₄), 3.0%; tri-iodothyronine (T₃), 3.4%; Tg, 1.9%; and anti-TPO, 7.1%. Fifty-four patients underwent thyroid ultrasound (US) for thyroid volume estimation. Eleven patients underwent a 24-h radioiodine uptake (RAIU).

A total of 70 patients were eligible to enter in the study. Two patients were excluded because of a previous diagnosis of hypothyroidism. Thus, 68 patients were included. Table 1 shows the clinical and laboratory characteristics of study participants. All study subjects displayed levels of T₄, FT₄, and T₃ in the normal range. Serum TSH was in the normal

range of 63/68 (92.6%) and slightly elevated in 5 patients (range 5.08–12.55 mU/l). The serum TSH levels before and after imatinib therapy, available for a subgroup of ten patients, were similar (2.39 (1.82–3.05) vs 2.71 (1.71–3.25) mU/l, $P=0.64$). Furthermore, there was no correlation between serum TSH levels and dose ($r=-0.043$, $P=0.73$), duration of therapy ($r=-0.084$, $P=0.50$), or cumulative dose of imatinib ($r=-0.105$, $P=0.39$). Because of a previous study report supporting thyroiditis in patients under sunitinib therapy (4, 7), Tg and anti-TPO were also measured. Serum Tg was at normal levels and only one patient displayed positivity for anti-TPO. Thyroid volume and RAIU were in the normal range. The power calculation of our study was the following: for correlations, considering an α error of 0.05 and a β error of 0.20, estimations of r values of 0.3, 0.4, and 0.5 resulted in calculated required samples of 84, 46, and 29 patients respectively (NCSS Statistical & Power Analysis Software 2007, Kaysville, UT USA).

Despite previous positive reports, here we found no influence of imatinib on thyroid function. The lack of correlation between TSH levels with dose, duration, or cumulative dose of imatinib therapy suggests that this drug has no adverse effect on thyroid function. In addition, the prevalence of subclinical hypothyroidism in this sample was ~10.0%, similar to that reported for our population (8).

Imatinib exerts its effects through inhibition of multiple TKs, including Bcr-Abl, platelet-derived growth factor receptors α and β , c-Fms, and c-kit (1). The increased demand for levothyroxine induced by imatinib in patients under levothyroxine replacement (6) might indicate increased peripheral metabolism of thyroid hormones. As suggested by others (6), induction of hepatic conjugation with glucuronates and sulfates would be a possible explanatory mechanism. Another potential explanation could be increased hormonal deiodination to reverse T₃ through enhanced deiodinase type 3 (D3) activity. Because both metabolic pathways would imply an increase in thyroid hormone output to overcome the increased peripheral clearance, it would be expected to find borderline-low values of T₄ and T₃ and borderline-high values of TSH in non-thyroidectomized

Table 1 Clinical and laboratory characteristics of the 68 patients under imatinib therapy.

Epidemiology	
Sex (men/women), <i>n</i> (%)	39 (57.3)/29 (42.7)
Age (years)	48.4 ± 17.6
White, <i>n</i> (%)	63 (92.6)
Time from diagnosis (months)	47 (21–74)
ECOG performance status, <i>n</i> (%)	
0	46 (67.6)
1	20 (29.4)
2	2 (2.9)
≥3	0 (0.0)
Imatinib therapy	
Duration (months)	23 (6–33)
Dose (mg)	400 (400–600)
Cumulative dose (g)	10.5 (2.0–17.9)
Thyroid function	
TSH (mU/l)	1.78 (1.28–3.19)
T ₄ (nmol/l)	114.5 ± 20.6
Free T ₄ (pmol/l)	16.2 ± 2.8
T ₃ (nmol/l)	1.60 ± 0.38
Thyroglobulin (ng/ml)	15.7 (10.6–31.7)
Positive anti-TPO, <i>n</i> (%)	1 (1.5)
Thyroid ultrasonography ^a	
Volume (ml)	8.7 ± 4.1
Radioiodine uptake ^b	
24 h (%)	15.7 ± 5.5

ECOG, Eastern Cooperative Oncology Group. Data are presented as mean ± s.d. or median (percentiles 25–75). The reference ranges for laboratory values are: T₄, 65.6–181.5 nmol/l (5.1–14.1 µg/dl); free T₄, 12.0–21.9 pmol/l (0.93–1.70 ng/dl); T₃, 1.23–3.07 nmol/l (80–200 ng/dl); and TSH, 0.4–4.5 mU/l. To convert T₄ values to micrograms per dl and free T₄ values to nanograms per dl, divide by 12.87. To convert T₃ values to nanograms per dl, divide by 0.01536. Radioiodine uptake is expressed as the percentage of the administered dose; reference values are 15–35%.

^a*n* = 54 patients for this variable.

^b*n* = 11 patients for this variable.

individuals. However, it does not seem to be the case, since all patients displayed normal T₄ and T₃ values. A reasonable explanation would be that imatinib interferes with the gastrointestinal absorption of LT₄, but this remains to be clarified.

It is interesting that previous studies with sunitinib have shown induction of hypothyroidism in nearly one-third of chronic users (4, 5). TSH suppression was demonstrated prior to the development of overt hypothyroidism in 6 out of 15 patients, suggesting that sunitinib induces hypothyroidism through a mechanism of destructive thyroiditis (4). Reduction in RAIU concomitant with elevation in TSH levels has also been reported, suggesting that reduction in thyroid iodine incorporation may be involved in sunitinib-induced hypothyroidism (9). The distinct patterns of TK inhibition presented by sunitinib or imatinib might explain their divergent effects on thyroid function. Of note, imatinib has inhibitory activity neither against vascular endothelial growth factor (VEGF) nor against EGF (1). Our study has some limitations such as sample size and lack of TSH values before imatinib therapy for all patients. However, the sample size was calculated to

detect correlations of moderate significance and previous TSH measurements would be critical if an association between imatinib and TSH had emerged from this study.

In conclusion, imatinib does not seem to be associated with hypothyroidism induction in non-thyroidectomized individuals. This information implies that routine screening of thyroid function in patients receiving imatinib should be precluded.

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