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 Clinicas 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). Inters assay 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 patients.
Imatinib therapy

The percentage of the administered dose; reference values are 15–35%. Radioiodine uptake is expressed as the

nanograms per dl, divide by 0.01536. Radioiodine uptake is expressed as the

that sunitinib induces hypothyroidism through a

demonstrated prior to the development of overt

size and lack of TSH values before imatinib therapy for

EGF(1). Our study has some limitations such as sample

note, imatinib has inhibitory activity neither against

explain their divergent effects on thyroid function. Of

inhibition presented by sunitinib or imatinib might

12.0–21.9 pmol/l (0.93–1.70 ng/dl); T3, 1.23–3.07 nmol/l (80–200 ng/dl);

free T4 values to nanograms per dl, divide by 12.87. To convert T3 values to

Thyroid ultrasonographya

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

day four by day 12. To convert T3 values to 

Thyroid ultrasonographya

were 8.7 ± 4.1

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free T4 values to nanograms per dl, divide by 12.87. To convert T3 values to

radioiodine uptakeb

24 h (%) 15.7 ± 5.5

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