



ORIGINAL ARTICLE

Evaluation of Thyroid Dysfunction during Imatinib Therapy in Chronic Myeloid Leukemia

Abolghasem Allahyari¹, Foroogh Salehi², Mostafa Kaboli³, Masoud Sadeghi^{4*}

1. Department of Hematology-Oncology, Emam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

2. Department of Endocrinology, Vali Asr Hospital, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran

3. Department of Internal Medicine, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran

4. Cancer Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

ARTICLE INFO

Article History:

Received: 10.10.2015

Accepted: 1.02.2016

Keywords:

Chronic myeloid leukemia

Imatinib mesylate

Thyroid dysfunction

Thyroid function tests

*Corresponding author:

Masoud Sadeghi,

Address: Cancer Research Center,

Kermanshah University of Medical

Sciences, Kermanshah, Iran

Email: sadeghi_mbrc@yahoo.com

ABSTRACT

Background: Imatinib mesylate is the first generation of Tyrosine kinase inhibitors (TKI) and highly effective in the treatment of chronic myeloid leukemia (CML). We aimed to evaluate thyroid function at baseline and at 1, 3, 6 and 12 months after initiation of Imatinib mesylate therapy in 20 newly diagnosed BCR-ABL positive CML patients.

Methods: This study was done during 2013-2014, 20 new cases with Philadelphia chromosome-positive CML without any underlying thyroid disorder or drug history interfering with Imatinib mesylate were enrolled. Thyroid function tests including serum Thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) were assessed at baseline and during follow-up.

Results: Mean age at diagnosis was 60.4 years. 14 (70%) patients were male. Mean value for TSH, FT4, FT3, Anti-TPO, and Anti-Tg before treatment were 2.82 mIU/L, 1.39 ng/dl, 325.50 ng/dl, 30.35 IU/ml and 39.40 IU/ml, respectively. The mean value for TSH, FT4, FT3 and Anti-TPO 1, 3, 6, and 12 months after initiation of Imatinib mesylate were not statistically significant.

Conclusion: Based on the results of the study, there was no significant change in thyroid function tests during treatment with Imatinib mesylate and all laboratory variables were in normal ranges.

Please cite this article as: Allahyari A, Salehi F, Kaboli M, Sadeghi M. Evaluation of Thyroid Dysfunction during Imatinib Therapy in Chronic Myeloid Leukemia. IJBC 2016; 8(1): 9-12.

Introduction

Chronic myeloid leukemia (CML) accounts for about 30% of all leukemias. It occurs in all age groups, 20% of patients are younger than 25 years.¹ Tyrosine kinase inhibitors (TKIs) block tyrosine kinase signaling pathways that modulate oncogenesis.² They exhibit vascular and antiangiogenic properties by interacting with VEGF.² TK proteins are a broad group of cell membrane proteins (about 500 different proteins) involved in important cellular activities such as proliferation, differentiation, and apoptosis. TKIs are new and small designed targeted molecules that are analog to ATP molecule structure

and arrive to compete with real ATP for binding to tyrosine part of TK molecule. Thus, they preclude TK phosphorylation via an inhibitory competitive replacement and cutting-off TK-dependent oncogenic pathways.³⁻⁵ The increased demand for levothyroxine induced by imatinib in patients who are receiving levothyroxine replacement therapy might indicate increased peripheral metabolism of thyroid hormones.⁶ Thyroid dysfunction is a known side effect of some tyrosine kinase inhibitors such as sunitinib and sorafenib⁷ while imatinib has been shown to induce hypothyroidism and increased requirement for levothyroxine in thyroidectomized patients.^{6,8} There are

few retrospective studies on CML patients treated with imatinib which have demonstrated conflicting effects on thyroid function tests.⁹ We have prospectively studied thyroid function tests at baseline and at 1, 3, 6 and 12 months after initiation of treatment with imatinib in 20 newly diagnosed BCR-ABL positive patients with CML.

Materials and Methods

This study was approved by Birjand University Ethics Committee, Birjand, Iran. In this study from February 2013 to August 2014, 20 new cases with Philadelphia chromosome-positive CML without any underlying thyroid disorder or any history of using drugs interfering with imatinib or having effect on thyroid function (Dexamethasone, Phenytoin, Carbamazepine, Rifampin and Phenobarbital) were enrolled. Thyroid function tests at baseline and during follow-up included serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg). Serum TSH, FT3, and FT4 were measured by an electrochemiluminescence immunoassay (ECLIA; Roche, Grenzach-Wyhlen, Germany); Anti-TPO and Anti-Tg by a luminescence immunoassay with time-resolved amplified cryptate emission technology (Brahms, Hennigsdorf, Germany) before and 1, 3, 6 and 12 months after initiation of imatinib therapy (400 mg per day). Serum samples were collected, handled, and analyzed according to internal standard operating procedures. Laboratory reference ranges were 0.27–4.20 mIU/L for TSH, 260–501 ng/dl for FT3, and 0.9–1.9 ng/dl for FT4. Upper limits for antibody positivity were >60 IU/ml for Anti-Tg and Anti-TPO.⁹

Results

The patients' mean age at diagnosis was 60.4 years. 14 (70%) patients were male and 6 (30%) were female. The mean values for TSH, FT4, FT3, Anti-TPO, and Anti-Tg before treatment were 2.82 mIU/L, 1.39 ng/dl, 325.50 ng/dl, 30.35 IU/ml, and 39.40 IU/ml, respectively (table 1). Mean values for TSH, FT4, FT3 and Anti-TPO 1, 3, 6 and 12 months after initiation of Imatinib were not statistically significant. There was a significant difference in mean values of Anti-Tg 1, 3, 6 and 12 months after initiation of treatment with imatinib ($P=0.014$, 0.008, 0.003 and 0.002, respectively).

Discussion

CML is the most common myeloproliferative disorder in adults with a characteristic cytogenetic abnormality

known as t(9;22).¹⁰ De Groot et al.⁶ reported the results of a study on 11 patients who had received imatinib (1 with gastrointestinal stromal tumor and 10 with *medullary thyroid carcinoma (MTC)*; eight of these patients had previously undergone thyroidectomy and were on thyroid hormone replacement therapy. Increased thyroid hormone requirements were observed while on imatinib therapy. In another study by de Groot et al.⁸ nine out of 15 advanced MTC patients who were treated with imatinib, had previously undergone total thyroidectomy and were on thyroid hormone replacement therapy, all them had increased thyroid hormone requirements while on therapy. On the other hand, patients with intact thyroid glands remained euthyroid while on imatinib. Therefore, both studies showed that all patients with intact thyroid glands receiving imatinib had no thyroid dysfunction. In a study from Desai et al.¹¹ on 42 patients treated with sunitinib for a median of 37 weeks (range, 10 to 167), 4 patients (10%) developed isolated TSH suppression and 7 patients (17%) experienced transient, mild TSH elevations. The risk for hypothyroidism increased with the duration of treatment with sunitinib. Six (40%) of 15 hypothyroid patients had suppressed TSH concentrations before developing hypothyroidism suggesting thyroiditis. Kim et al.⁹ retrospectively reviewed thyroid function tests in 10 patients who were treated with dasatinib, 2 patients were on levothyroxine prior to starting therapy, 5 patients developed hypothyroidism (4 subclinical, 1 clinical), and two patients had subclinical hyperthyroidism, none of which required treatment. Dora et al.¹² found no adverse effect of imatinib on thyroid function and lack of correlation between TSH levels with dose, duration, or even cumulative dose of imatinib therapy suggests that this drug has no side effect on thyroid function.

The mechanism of imatinib-induced subclinical or clinical hypothyroidism was stimulation of T3 and T4 clearance owing to elevated activity of liver microsomal enzyme, uridine-diphosphate-glucuronyltransferase (UGTs), which needed to be stabilized.¹³ Sorafenib has been associated with hypothyroidism in patients with previously normal thyroid function, with an incidence of 18% in one study¹⁴ and 67% in another study.¹⁵ Other TKIs have also been associated with thyroid disease in patients with previously intact thyroid function.⁹ In a retrospective study of 64 patients treated for CML, hypothyroidism was seen in 13%, 50%, and 22% of patients treated with imatinib, dasatinib, or nilotinib, respectively.⁹ The incidence of preceding transient thyrotoxicosis was also high suggesting a phase of thyroiditis preceding the

Table 1: Thyroid tests in patients with chronic myeloid leukemia before and after Imatinib therapy

Thyroid tests	Before treatment with imatinib	1 month after treatment	3 months after treatment	6 months after treatment	12 months after treatment
FT3, ng/dl	325.5	333.5	333	321	312
FT4, ng/dl	1.39	1.36	1.22	1.33	1.34
TSH, mIU/l	2.82	2.67	2.88	2.94	3.02
Anti-TPO, IU/ml	30.35	29.45	32.7	33.05	33.15
Anti-Tg, IU/ml	39.4	50.75*	55.85*	60.3*	56.3*

*P value<0.05 was significant; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; Anti-TPO, anti-thyroid peroxidase; Anti-Tg, anti-thyroglobulin

loss of function.⁹ The main mechanism of TKI-induced hypothyroidism is unclear. Rare cases of thyrotoxicosis preceding the development of hypothyroidism suggest that there is a preceding thyroiditis. Some suggestions for the mechanism of hypothyroidism associated with TKIs include direct toxic effects on thyrocytes, reduced TPO activity,¹⁶ impaired iodine uptake,¹⁷ or stimulation of Hashimoto thyroiditis,¹⁸ although Hashimoto thyroiditis is improbable to be the main mechanism because of the low prevalence of Anti-TPO antibodies in patients with sunitinib-induced hypothyroidism.^{17,19} The most likely explanation is that the thyroid dysfunction is related to the effects of these factors on tyrosine kinases involved in vascular function such as VEGFR. This could cause attenuation of the thyroid blood flow to this extremely vascular gland. If the blood flow decreases rapidly, an ischemic thyroiditis could result leading to a transient period of thyrotoxicosis. If the decreased blood flow develops more slowly, gradual thyroid destruction may occur with resulting hypothyroidism.¹⁴ Supporting evidence for this theory includes the finding that thyroid cells express VEGF and VEGFR mRNA and studies on mice have shown glandular capillary regression with TKI exposure.²⁰ Two recent case reports demonstrated reduced thyroid volume and vascularity by doppler ultrasound,^{17,21,22} with rapid increase in size of the thyroid following cessation of sunitinib. The reduced thyroid volume (because of reduced blood flow) may also explain the impaired radioactive iodine uptake *in vivo*¹⁷ but not *in vitro*.²³

Conclusion

Based on results of this study, there was no significant change on thyroid function tests during imatinib therapy and all variables were within normal ranges. However, larger studies with larger sample size are recommended to prove imatinib-induced hypothyroidism.

Conflict of Interest: None declared.

References

1. Payandeh M, Sadeghi M, Sadeghi E. Treatment and Survival in Patients with Chronic Myeloid Leukemia in a Chronic Phase in West Iran. *Asian Pac J Cancer Prev*. 2015;16(17):7555-9.
2. Le Tourneau C, Faivre S, Raymond E. New developments in multitargeted therapy for patients with solid tumours. *Cancer Treat Rev*. 2008;34(1):37-48.
3. Daub H. Kinase inhibitors: narrowing down the real targets. *Nat Chem Biol*. 2010 Apr;6(4):249-50.
4. Illouz F, Laboureaux-Soares S, Dubois S, Rohmer V, Rodien P. Tyrosine kinase inhibitors and modifications of thyroid function tests: a review. *Eur J Endocrinol*. 2009;160(3):331-6.
5. Rios MB, Ault P. Identification of side effects associated with intolerance to BCR-ABL inhibitors in patients with chronic myeloid leukemia. *Clin J Oncol Nurs*. 2011;15(6):660-7.
6. de Groot JW, Zonnenberg BA, Plukker JT, van Der Graaf WT, Links TP. Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther*. 2005;78(4):433-8.
7. Riesenbeck LM, Bierer S, Hoffmeister I, Köpke T, Papavassilis P, Hertle L, et al. Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. *World J Urol*. 2011;29(6):807-13.
8. de Groot JW, Zonnenberg BA, van Ufford-Mannesse PQ, de Vries MM, Links TP, Lips CJ, et al. A phase II trial of imatinib therapy for metastatic medullary thyroid carcinoma. *J Clin Endocrinol Metab*. 2007;92(9):3466-9.
9. Kim TD, Schwarz M, Nogai H, Grille P, Westermann J, Plöckinger U, et al. Thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Philadelphia chromosome-positive chronic myeloid leukemia. *Thyroid*. 2010;20(11):1209-14.
10. Payandeh M, Sadeghi E, Khodarahmi R, Sadeghi M. Appearance and Disappearance of Chronic Myeloid Leukemia (CML) in Patient with Chronic Lymphocytic Leukemia (CLL). *Int J Hematol Oncol Stem Cell Res*. 2014;8(4):49-53.
11. Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med*. 2006;145(9):660-4.
12. Dora JM, Leie MA, Netto B, Fogliatto LM, Silla L, Torres F, et al. Lack of imatinib-induced thyroid dysfunction in a cohort of non-thyroidectomized patients. *Eur J Endocrinol*. 2008;158(5):771-2.
13. de Groot JW, Links TP, van der Graaf WT. Tyrosine kinase inhibitors causing hypothyroidism in a patient on levothyroxine. *Ann Oncol*. 2006;17(11):1719-20.
14. Tamaskar I, Bukowski R, Elson P, Ioachimescu AG, Wood L, Dreicer R, et al. Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. *Ann Oncol*. 2008;19(2):265-8.
15. Miyake H, Kurahashi T, Yamanaka K, Kondo Y, Muramaki M, Takenaka A, et al. Abnormalities of thyroid function in Japanese patients with metastatic renal cell carcinoma treated with sorafenib: a prospective evaluation. *Urol Oncol*. 2010;28(5):515-9.
16. Wong E, Rosen LS, Mulay M, Vanvugt A, Dinolfo M, Tomoda C, et al. Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. *Thyroid*. 2007;17(4):351-5.
17. Mannavola D, Coco P, Vannucchi G, Bertuelli R, Carletto M, Casali PG, et al. A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. *J Clin Endocrinol Metab*. 2007;92(9):3531-4.
18. Alexandrescu DT, Popoveniuc G, Farzanmehr H, Dasanu CA, Dawson N, Wartofsky L. Sunitinib-associated lymphocytic thyroiditis without circulating antithyroid antibodies. *Thyroid*. 2008;18(7):809-12.
19. Rini BI, Tamaskar I, Shaheen P, Salas R, Garcia J, Wood L, et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib.

- J Natl Cancer Inst. 2007;99(1):81-3.
20. Kamba T, Tam BY, Hashizume H, Haskell A, Sennino B, Mancuso MR, et al. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. *Am J Physiol Heart Circ Physiol*. 2006;290(2):H560-76.
 21. Makita N, Miyakawa M, Fujita T, Iiri T. Sunitinib induces hypothyroidism with a markedly reduced vascularity. *Thyroid*. 2010;20(3):323-6.
 22. Rogiers A, Wolter P, Op de Beeck K, Thijs M, Decallonne B, Schöffski P. Shrinkage of thyroid volume in sunitinib-treated patients with renal-cell carcinoma: a potential marker of irreversible thyroid dysfunction? *Thyroid*. 2010;20(3):317-22.
 23. Salem AK, Fenton MS, Marion KM, Hershman JM. Effect of sunitinib on growth and function of FRTL-5 thyroid cells. *Thyroid*. 2008;18(6):631-5.