Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Does thyroid dysfunction happen in CML patients receiving Imatinib for treatment?

Hossein Rahimi (MD)[1], Zahra Mazloum Khorasani (MD)[2], Saeedeh Shariati (MD)[3*]

[1]*Department of Hematology& Oncology, Quaem hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Endocrine Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLE INFO

Article type
Review article

Article history
Received: 4 Mar 2014
Revised: 15 Apr 2014
Accepted: 11 May 2014

Keywords
Chronic myelogenous leukemia
Imatinib
Thyroid dysfunction

ABSTRACT

Chronic myelogenous leukemia is a myeloproliferative disorder presenting with anemia, elevated blood granulocytosis and the presence of immature granulocytes, basophilia, frequently thrombocytosis and spleen enlargement. The diagnosis is stabilized by hematopoietic stem cell expressing a fusion gene (BCR/ABL) resulted from translocation of 9 and 22 chromosomes. The products of this gene play a central role in developing chronic myelogenous leukemia including maintenance of chronicity and/or progress to accelerated phase and or blastic crisis. Imatinib is the first generated tyrosine kinase Inhibitor, which prevents ATP binding to a specific situation of tyrosine kinase molecules that are involved in phosphorylation of membranous proteins and activation of the pathways that are necessary for tumor cell survey and proliferation. Therefore, tyrosine kinase inhibitor inhibits signaling proteins, which are responsible for tumor growth, invasion, angiogenesis and even metastasis. Although tyrosine kinase inhibitor are specific targeted-designed compounds, every agent interacts with many kinds of tyrosine kinases and produces many unwanted effects. One of the undesirable adverse effects is thyroid dysfunction. The first reported article about tyrosine kinase inhibitor-induced thyroid dysfunction published in 2005 and since then few studies have demonstrated thyroid disturbances ranging from subclinical thyroid dysfunctions to overt clinically thyroid disorders during tyrosine kinase inhibitor therapy. This review attends to summarize only imatinib-induced thyroid disturbances in CML patients with positive Philadelphia chromosome in recent years.

Please cite this paper as:
Rahimi H, Mazloum Khorasani Z, Shariati S. Does imatinib cause thyroid function alterations in CML patients receiving it for treatment? Rev Clin Med. 2015;2(2):92-95.

Introduction

A reciprocal translocation between 9 and 22 chromosomes causes a fusion-gene combination, BCR/ABL gene, expressed in hematopoietic stem cell. Clonal expansion of these cells is the main event leading to developing CML. Protein products related to activation of this combined gene are active tyrosine kinases responsible for starting and chronicity of CML. Chronic phase of CML can progress to an accelerated and/or blast crisis phase if leaved untreated, almost in a 4-year duration, frequently was happened in pre-imatinib era (1-5). Tyrosine kinase proteins (Tks) are a broad group of cell membrane proteins (about 500 different proteins) involved in important cellular activity such as proliferation, differentiation and apoptosis. Tyrosine kinase inhibitors (TKIs) are new and small designed targeted molecules

***Corresponding author:** Saeedeh Shariati.*
Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
***E-mail:** mkerachian@yahoo.com*
***Tel:** 051-38455790*

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 (6-8). TKIs have offered excessive benefits in therapeutic strategies of malignant diseases and they can yield less toxicity compared to conventional chemotherapeutic agents administered for malignancies owing to their inherent selective targeting (9-11). Because each TKI agent potentially can interact with several different TK-dependent signaling pathways in various tissues, rationally several kinds of unwanted side effects can occur during TKI therapy. Among them endocrinological disturbances such as thyroid dysfunction are discussed here (7,9,12). Imatinib was approved essentially as a new treatment for CML, interacts with BCR/ABL proteins (a cell membrane receptor TK), PDGFR (platelet-derivative growth factor receptor) and with KIT (non-receptor combined TK), both the latest ones are responsible for thyroid and other endocrinologic side effects (11,12).

Because thyroid disturbances induce adverse effects that complicate management of the patients with CML, it seems that the relation between the imatinib and thyroid disorders should be investigated. In this study, we review different articles about imatinib-induced thyroid disturbances in CML patients with positive Philadelphia chromosome.

Data collection was performed by searching through PubMed. The investigated key words included Imatinib, CML, chromosome-positive philadelphia and tyrosine kinase inhibitors. Among concerned articles founded in our search, two articles had evaluated imatinib-induced hypothyroidism in Ph-positive CML cases. But in this article, we reviewed the alterations of thyroid function tests due to imatinib with concentrating on CML patients.

Literature review

At firs,t Imatinib-induced thyroid alterations were studied by de Groot et al. in 2005, who applied imatinib in 25 patients divided in 2 separated groups. Group A included 10 subjects with medullary thyroid carcinoma and one patient with GIST (gastrointestinal stromal tumor). Group B contained 15 patients with metastatic medullary thyroid cancer (MTC) in another time. The results were the same for both groups. TSH was markedly more elevated in patients undergoing thyroidectomy (athyroid) than patients with thyroid in situ. In patients with intact thyroid gland, modifications were limited to subclinical states. Any hypothyroid patient needed to increase dose of levothyroxine replacement therapy by 210% (13,14). All of these effects disappeared immediately after imatinib discontinuation.

All of the quoted results were shown in Dora et al. study in which 68 CML patients treating with imatinib, met no hormonal alterations of thyroid. They all were thyroid in situ (15).

The main mechanism of imatinib-induced (sub) clinical hypothyroidism as suggested by de-Groot, was the stimulation of T3 and T4 clearance owing to elevated activity of liver microsomal enzyme, uridine-diphosphate-glucuronyltransferase (UGTs), which needed to be stabilized (14,16).

In another study, Druker et al. conducted a long-period prospective study to assess and compare the efficacy of imatinib versus interferon alpha plus cytarabin in CML. In this study, 553 patients received imatinib for 60 months. One of the designed goals in this long-time follow-up was the recognition of imatinib adverse effects. Druker et al. did not mention any thyroid modifications in this evaluation (17).

By the same method, imatinib (in 260 patients) was investigated for its efficacy compared with dasitinib (in 259 patients) in a 12-month period prospectively in a multinational study driven by Kantarjian et al. They did not talk about thyroid dysfunction in their published article neither for imagine nor dasitinib (18).

In the study of Kim et al., thyroid malfunction was reported in 25% of patients during imatinib therapy in Philadelphia chromosome-positive CML patients (19).

In the most recent published cohort article, 30 patients with Philadelphia chromosome-positive CML who received imatinib were evaluated for thyroid abnormalities in 6-month duration by Ghalaut et al. In this prospective study, imatinib did not reveal any noticeable effect on thyroid action but it might be possible to find some thyroid function test abnormality (20). Despite the former studies, only Kim and Ghalaut studies were carried out among chromosome-positive Philadelphia CML cases and evaluated imatinib-induced thyroid laboratory alterations in these patients.

Major studies conducting in recent years are summarized in Table 1.

Conclusion

Although performed studies failed to show a significant relationship between imatinib and thyroid dysfunction, it seemed that thyroid functional monitoring was strongly recommended before, during and even after the termination of imatinib therapy courses even for previously euthyroid patients. Levothyroxine replacement

Table 1. The incidence of TKI-induced thyroid abnormalities

Autheor (Reference)	Tumor Type	TKI used	Number of patients	Number of patients with hypothyroidism (%)	Number of patients with altered TFTs (%)
Desae (21)	GIST*	Sunitinib	42	15 (36)	26 (62)
Rini (22)	RCC**	Sunitinib	66	(84)	(85)
Schoeffeki (23)	GIST/RCC	Sunitinib	33	21 (53)	ND
Wong (24)	GIST/Other	Sunitinib	40	21 (53)	ND
Mannavola (25)	GIST	Sunitinib	24	17 (71)	ND
Tamaskar (26)	RCC	Sorafenib	39	7 (8)	16(43)
Kim (19)	CML***	Imatinib	Not found	None	(25)
Dora (15)	CML	Imatinib	68	None	(7)
Groot (13,14)	MTC	Imatinib	26	(100)	(100)
Ghaluat (20)	CML	Imatinib	30	None	2(10)

*GIST: Gastrointestinal stromal tumor; **RCC: Renal cell carcinoma; ***CML: Chronic myelogenous leukemia; **** MTC: Medullary thyroid carcinoma

almost always should be considered in cases undergoing thyroidectomy during imatinib therapy. The increase of levothyroxine doses might be necessary for the improvement of quality of life in these patients.

CML occur predominantly in middle to old age individuals. In these patients, the prevalence of hypothyroidism is much more than other age groups. Cardinal manifestations of hypothyroidism are generalized weakness and fatigue, edema as general nonspecific symptom related to primary hematologic disease, which are indistinguishable from hypothyroid state. These are diagnostic challenges that clinical practitioners have to face.

Because of the small sample sizes in imatinib and thyroid disturbance studies, further investigations are needed to determine the real effects of imatinib on thyroid functions.

Acknowledgement

We would like to thank Clinical Research Development Center of Ghaem Hospital for their assistant in this manuscript. This study was supported by a grant from the Vice Chancellor for Research of the Mashhad University of Medical Sciences for the research project as a medical student thesis with approval number of 2855-T.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Liesveld J, Lichtman M. Chronic myelogenous leukemia and related disorders. In: Kaushanksy K, Lichtman M, Beutler E, Kipps T, Seligsohn U, Prchal J, editors. Williams Hematology. New York: McGraw-Hill; 2010. p. 1331-1379.
2. Kavalerchik E, Goff D, Jamieson CH. Chronic myeloid leukemia stem cells. J Clin Oncol. 2008;26:2911-2915.
3. Savona M, Talpaz M. Getting to the stem of chronic myeloid leukaemia. Nat Rev Cancer. 2008;8:341-350.
4. Wetzler M, Byrd J, Bloomfield C. Acute and Chronic Myeloid Leukemia. In: Kasper D, Braunwald E, Fauci A, Hauser S, Longo D, Jameson J, editors. Harrison's Principles of Internal Medicine. 16th ed. New York: McGRAW - HILL Co; 2005. p. 631-641.
5. Garcia-Manero G, Faderl S, O'Brien S, et al. Chronic myelogenous leukemia: a review and update of therapeutic strategies. Cancer. 2003;98:437-457.
6. Daub H. Kinase inhibitors: narrowing down the real targets. Nat Chem Biol. 2010;6:249-250.
7. Illouz F, Laboureau-Soares S, Dubois S, et al. Tyrosine kinase inhibitors and modifications of thyroid function tests: a review. Eur J Endocrinol. 2009;160:331-336.
8. 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;15:660-667.
9. Lodish MB, Stratakis CA. Endocrine side effects of broad-acting kinase inhibitors. Endocr Relat Cancer. 2010;17:R233-R244.
10. Le Tourneau C, Faivre S, Raymond E. New developments in multitargeted therapy for patients with solid tumours. Cancer Treat Rev. 2008;34:37-48.
11. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med. 2005;353:172-187.
12. Nurmio M, Kallio J, Toppari J, et al. Adult reproductive functions after early postnatal inhibition by imatinib of the two receptor tyrosine kinases, c-kit and PDGFR, in the rat testis. Reprod Toxicol. 2008;25:442-446.
13. de Groot JWB, Zonnenberg BA, Plukker JT, et al. Imatinib induces hypothyroidism in patients receiving levothyroxine. Clin Pharmacol Ther. 2005;78:433-438.

14. De Groot J, Links T, Van der Graaf W. Tyrosine kinase inhibitors causing hypothyroidism in a patient on levothyroxine. Ann Oncol. 2006;17:1719-1720.
15. Dora JM, Leie MA, Netto B, et al. Lack of imatinib-induced thyroid dysfunction in a cohort of non-thyroidectomized patients. Eur J Endocrinol. 2008;158:771.
16. Wu S-y, Green WL, Huang W-s, et al. Alternate pathways of thyroid hormone metabolism. Thyroid. 2005;15:943-958.
17. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355:2408-2417.
18. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362:2260-2270.
19. Kim TD, Schwarz M, Nogai H, et al. Thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Philadelphia chromosome-positive chronic myeloid leukemia. Thyroid. 2010;20:1209-1214.
20. Ghalaut VS, Prakash G, Bala M, et al. Imatinib and Thyroid Dysfunction in BCR-ABL Positive CML Patients. Am J Cancer Ther Pharmacol. 2013;1:1-7.
21. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med. 2006;145:660-664.
22. Rini BI, Tamaskar I, Shaheen P, et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst. 2007;99:81-83.
23. Schoeffski P, Wolter P, Himpe U, et al. Sunitinib-related thyroid dysfunction: a single-center retrospective and prospective evaluation. J Clin Oncol. 2006;24:3092.
24. Wong E, Rosen LS, Mulay M, et al. Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. Thyroid. 2007;17:351-355.
25. Mannavola D, Coco P, Vannucchi G, et al. A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. J Clin Endocrinol Metab. 2007;92:3531-3534.
26. Tamaskar I, Bukowski R, Elson P, et al. Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. Ann Oncol. 2008;19:265-268.