Journal of Cancer Science & Treatment
JCST, 2(3): 150-154
www.scitcentral.com

ISSN: 2641-7472

Original Research Article: Open Access

Imatinib Therapy Induced Thyroid Dysfunction in Chronic Myeloid Leukemia Patients (Hospital Based Analytical Study)

Mai Elzahry* **and Mohamed Wahman**

*Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, South Valley University, Qena, Egypt.

Received January 24, 2020; Revised February 5, 2020; Accepted February 7, 2020

ABSTRACT

Background: Tyrosine kinase inhibitors have become more commonly used as targeted therapy for variable types of malignancies. Imatinib, is one of the tyrosine kinase inhibitors, which showed a good response in the treatment of chronic myeloid leukemia (CML). One of the common adverse effects of Imatinib is thyroid dysfunction.

Aim of work: Our aim was to assess the thyroid dysfunction hazards during Imatinib therapy on chronic myeloid leukemia patients in a retrospective manner.

Results: Out of 30 patients, 14 were male (46.7%) and 16 (53.3%) were female with a mean age of 49±12.4 years. 10 patients with pre-existing hypothyroidism were excluded. 9 out of 20 patients (45%) only expressed hypothyroidism (2 patients expressed clinically by fatigue and edema (22%), 4 (44%) showed subclinical hypothyroidism with a high TSH level, while the other 3 patients (33%) showed autoimmune thyroiditis confirmed by increased antithyroid peroxidase (TPO) level. Statistically, there was a significant relation between the occurrence of undesirable hypothyroidism and duration of Imatinib therapy (P-value=0.000).

Conclusion: This study showed significant thyroid dysfunction during the long duration of imatinib therapy. We recommend further studies in a prospective manner with the large size of the sample and longer duration of follow-up to detect further changes.

Keywords: Imatinib therapy, Thyroid dysfunction, Chronic myeloid leukemia**,** Hospital based analytical study

Abbreviations: TKI: Tyrosine kinase inhibitors; CML: Chronic myeloid leukemia; Anti-TPO: Anti-thyroid anti-peroxidase

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) are specific conjugates that affect TK-targeted oncogenic cycles. They are encouraging tools for the treatment of variable malignant diseases with high selective inhibition [1].

These agents eventually provide a relatively excellent therapeutic target with diminished toxicity in comparison with conventional chemotherapy. However, as we gain experience with these compounds, we are becoming aware of important side effects [2].

Imatinib is one of the first TKIs which show effectiveness in the treatment of chronic myelogenous leukemia (CML) [3]. Imatinib are administered orally and cause many toxic effects including fatigue, hypertension, rash, etc.). In addition to endocrine-related side effects of these agents including disturbances in thyroid function, gonadal dysfunction, alteration of fetal development, glucose, bone metabolism and adrenal dysfunction [4].

There are limited data on thyroid disturbances during imatinib therapy, so this current study will assess the occurrence of the thyroid-related toxic effects associated with imatinib in a retrospective manner in order to bring the clinicians in this field up to date with the hazards of the therapy.

Corresponding author: Mai Elzahry, C/O Dr.Rifat Elzahry, Department of Mechanical Engineering, Faculty of Engineering, Assiut University, Egypt, Tel: +2 01010720929; E-mail: mai.rifat@hotmail.com

Citation: Elzahry M & Wahman M. (2020) Imatinib Therapy Induced Thyroid Dysfunction in Chronic Myeloid Leukemia Patients (Hospital Based Analytical Study). J Cancer Sci Treatment, 2(3): 150-154.

MATERIALS & METHODS

This is clinical study on 30 patients of CML with positive Philadelphia chromosome in chronic phase were involved in this hospital-based study at our Department, the data collected retrospectively from the registration unit in the Department of Clinical Oncology and Nuclear Medicine, between December 2016 and December 2019.

Aim of the paper was to assess the current status concerning the hazards of Imatinib therapy on the development of thyroid dysfunction.

Eligibility

After taking the Ethical Review Committee approval and informed consent from each patient before participation in the study, only 30 cancer patients met the following eligibility criteria were selected carefully:

1. Histologically proven CML with Philadelphia chromosome positive in chronic phase with no other evidence of distant metastases at the thyroid gland.

2. Who were euthyroid clinically (with normal hormonal profiles) preceding treatment with Imatinib. Patients with past history of any thyroid problems, on any thyroid therapy or any medications that may affect thyroid function, like; steroids, were excluded. Normal TFT were defined as; (TSH) ≤ 4.2 mIU/L; (FT4) 12.5–22 pmol/L and (T3) between 3.1 and 5.5 pmol/L.

Imatinib therapy & thyroid function assessment

All patients enrolled in this study, received imatinib orally as a first-line treatment on a standard schedule (initial dose 400 mg/ml, in a continuous manner). For the purpose of the study, total thyroid profiles TSH, Free T4, Free T3, Anti thyroid peroxidase (Anti TPO), and Anti thyroglobulin (Anti Tg) were obtained from each patient before and after 4 and 24 weeks for assessment of toxicity and remission, respectively).

Based on the last follow up, patients with hypothyroidism expressed by (high level of TSH and/or low FT3/FT4 while patients with thyroiditis expressed with high level of Anti-TPO.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 16. Data presented as the mean±SD Pearson's correlation was used to assess the relationships between two variables to assess its strength as well as linear regression test. The p-value <0.05 was accepted to be statistically significant.

RESULTS

In this retrospective study, 30 patients with known diagnosed CML Philadelphia chromosome positive in chronic phase were enrolled. 10 patients with preexisting hypothyroidism were excluded, reduced the total number to 20 eligible patients, 9 were male (45%) and 11 (55%) were female with a mean age of 50 ± 11.9 years **(Table 1)**.

The major percentage of the patients received imatinib therapy was 35% over 4 months while the lowest percentage among patients received Imatinib therapy was 5% over 2.6.8.11 months **(Table 2)**.

Table 1. Demographic characteristics.

Personal Characteristics		
Age: (years)		
• Mean ± SD	**50±11.9**	
• Range	**33-68 y**	
Sex:	**n.**	**%**
Male	**9/20**	**45**
Female	**11/20**	**55**

**Descriptive test*

9 out of 20 patients (45%) only expressed hypothyroidism (2 patients expressed clinically by fatigue and edema (22%), 4 (44%) showed subclinical hypothyroidism with a high TSH level, while the other 3 patients (33%) showed autoimmune thyroiditis confirmed by increased Antithyroid Anti-peroxidase (TPO) level.

Statistically, there is a high significant correlation between the undesirable hypothyroidism occurrence and duration of Imatinib therapy and 59% could be explained (R factor=0.76, R square=0.59, P-value=0.000) **(Table 3)**.

A linear regression test was done to assess if there is a correlation between the hypothyroidism occurrence and the duration of the Imatinib therapy, it revealed a good linear correlation **(Figure 1)**.

DISCUSSION

Although the mechanism by which TKIs cause thyroid dysfunction remains unclear. A limited number of studies have been performed to try to characterize the mechanism of

Table 2. Frequency of Imatinib therapy in study population.

Month	Frequency	Percent (%)
2	1	5
3	2	10
4	7	35
5	2	10
6	1	5
7	2	10
8	1	5
11	1	5
14	3	15
Total	20	100

Table 3. The correlation between the hypothyroidism occurrence and imatinib therapy duration.

Imatinib therapy duration (Month)	Hypothyroidism existence	Correlation coefficient factor (r)	R square	P-value
4	+	0.76	0.59	**0.000***
14	-			
3	-			
8	+			
6	+			
5	-			
4	-			
7	+			
4	-			
14	+			
4	-			
3	+			
7	+			
2	-			
11	+			
5	+			
4	-			
14	+			
4	-			

*+: hypothyroidism, -: no hypothyroidism, *Statistically significant difference (p< 0.05)*

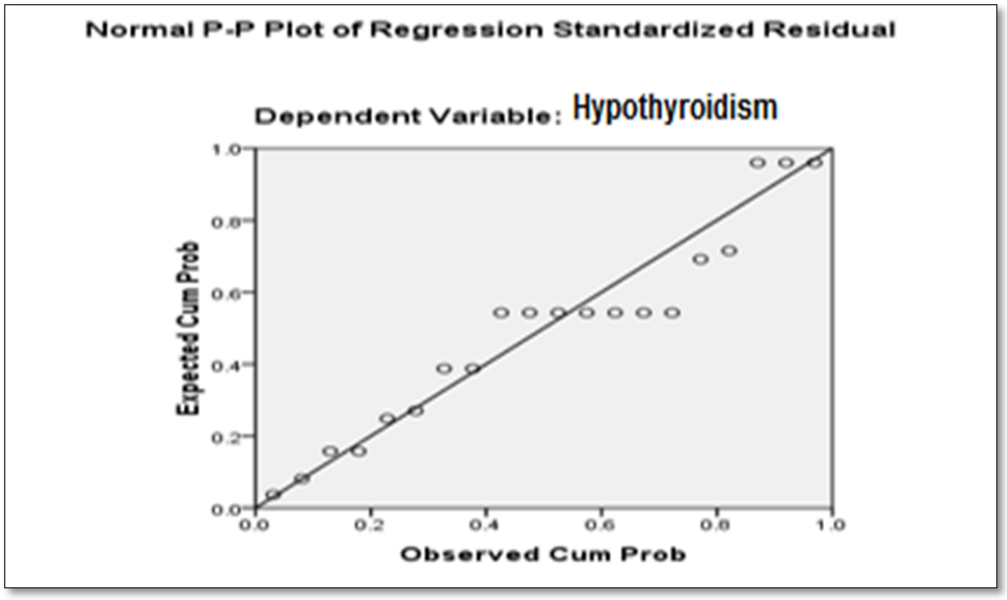

Figure 1. Linear regression diagram between the dependent variable "hypothyroidism" and independent variable "imatinib therapy duration".

TKI induced hypothyroidism, mostly coming from de Groot's group [5,6]. 15 patients were treated with Imatinib and hypothyroidisms expressed only in nine patients while the others kept a normal thyroid hormone profile during the Imatinib therapy. Kim et al. [7], also reported alterations in thyroid function tests in 25% of patients received Imatinib. In our study which has nearly similar results as compared to de Groot groups, 9 out of 20 patients expressed clinical/subclinical hypothyroidism proved by elevated TSH and or low T3, T4.

Our study revealed significant changes at levels of T3, T4 and TSH during imatinib therapy at the time of follow up beyond 5 months, one of the designed goals in this long-time follow-up was the recognition of imatinib adverse effects. Druker et al. [8] did not mention any thyroid modifications in this evaluation.

Dora et al. [9] performed another study in 2008, all of the cases of CML on imatinib therapy underwent long follow up for more than six months, none of them showed thyroid dysfunction as well as in Mashahdi study in 2014, which showed normal levels of thyroid hormones, Anti TPO, before and during imatinib therapy [10].

Our study detected only 3 patients out of 20 with autoimmune thyroiditis proved by elevated level of TPO, other studies also reported the effects of other tyrosine kinase inhibitors, especially sunitinib on thyroid function. The abnormalities included autoimmune thyroiditis, transient or permanent hypothyroidism and increased dose of levothyroxine [7, 11, 12].

In spite of these significant changes of TFT among the patients during imatinib therapy, none of them induce to discontinue imatinib or induce levothyroxine treatment, all of these effects disappeared immediately after imatinib discontinuation. The main mechanism of imatinib-induced sub/or clinical hypothyroidism is still unknown but may be due to apoptosis which manifests initially by a destructive thyroiditis and then gradually progresses to be atrophic one.

CONCLUSION

As a result of this study with other relevant studies, which reported significant changes in thyroid function during long follow up duration of imatinib, it is now recommended that all patients starting therapy with TKIs have their thyroid function test before and during imatinib therapy.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Krause DS, Van Etten RA (2005) Tyrosine kinases as targets for cancer therapy. N Engl J Med 353: 172-187.

2. Zhang J, Yang PL, Gray NS (2009) Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer 9: 28-39.

3. Jabbour E, Cortes JE, Giles FJ, O'Brien S, Kantarjian HM (2007) Current and emerging treatment options in chronic myeloid leukemia. Cancer 109: 2171-2181.

4. Widakowich C, de Castro G Jr, de Azambuja E, Dinh P, Awada A (2007) Review: Side effects of approved molecular targeted therapies in solid cancers. Oncologist 12: 1443-1455.

5. de Groot JW, Zonnenberg BA, Plukker JT, van Der Graaf WT, Links TP (2005) Imatinib induces hypothyroidism in patients receiving levothyroxine. Clin Pharmacol Ther 78: 433-438.

6. de Groot JW, Zonnenberg BA, van Ufford-Mannesse PQ, de Vries MM, Links TP, et al. (2007) A phase II trial of imatinib therapy for metastatic medullary thyroid carcinoma. J Clin Endocrinol Metab 92: 3466-3469.

7. Kim TD, Schwarz M, Nogai H, Grille P, Westermann J, et al. (2010) Thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Philadelphia chromosome-positive chronic myeloid leukemia. Thyroid 20: 1209-1214.

8. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, et al. (2006) Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 355: 2408-2417.

9. Dora JM, Leie MA, Netto B, Fogliatto LM, Silla L, et al. (2008) Lack of imatinib-induced thyroid dysfunction in a cohort of non-thyroidectomized patients. Eur J Endocrinol 158: 771-772.

10. Mashhadi MA, Kaykhaei MA, Mohammadi M, Hashemi M, Mohamadi Fatide T (2014) Imatinib therapy in chronic myelogenous leukemia and thyroid function tests. Int J Hematol Oncol Stem Cell Res 8: 20-23.

11. Desai J, Yassa L, Marqusee E, George S, Frates MC, et al. (2006) Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 145: 660-664.

12. Wolter P, Stefan C, Decallonne B, Dumez H, Bex M, et al. (2008) The clinical implications of sunitinib-induced hypothyroidism: A prospective evaluation. Br J Cancer 99: 448-454.