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A Study Of Thyroid Dysfunction Caused By Tyrosine Kinase Inhibitors In Patients With Philadelphia Chromosome Positive Chronic Myeloid Leukemia

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ABSTRACT

Background –Tyrosine kinase inhibitors (TKI) are used as the frontline drugs in the management of patients with chronic myeloid leukemia (CML). The aim of the study was to find the effect of tyrosine kinase inhibitors on thyroid function in patients with Philadelphia chromosome positive CML.
Materials & Methods – A retrospective observational study was conducted in 100 patients attending the hematology OPD of a tertiary care hospital. Pre and post treatment thyroid profile were done for all the patients and the effect of TKI on thyroid profile was assessed.
Results – There was a male predominance (79%) in the study population. 64% of the patients were in the age group of 41 to 60 years. There was statistically significant raise in the serum TSH and fall in the T3 and T4 values after the completion of treatment of 6 months (P < 0.00001). At the end of 6-month yyytreatment period, 9% of patients had overt hypothyroidism, 6% of patients had subclinical hypothyroidism and the remaining were euthyroid. (P = 0.0042)
Conclusion – The presence of statistically significant increase in the TSH levels and the increase in presence of thyroid dysfunction makes it vital to screen for thyroid abnormalities in patients with CML. Especially in patients with subclinical hypothyroidism, strict regular follow up is recommended to prevent overt hypothyroidism in them.
Keywords – CML, Thyroid dysfunction, Tyrosine kinase inhibitors, TKI, Ph chromosome, subclinical hypothyroidism

1. INTRODUCTION

Chronic myeloid leukemia (CML), otherwise known as chronic myelogenous leukemia, is defined as a clonal disease that results from an acquired genetic variation in a pluripotent haemopoietic stem cell that leads to an increase in the myeloid cells. CML is characterised by a cytogenetic abnormality which is due to the reciprocal translocation between Abl-proto-oncogene on chromosomes 9 and truncated Bcr - breakpoint cluster region on 22. (Faderl S et al., 1999)

The main stay for the treatment of patients with CML is Tyrosine kinase inhibitors (TKI) which are classified as molecular targeted therapy. The mechanism of action of TKIs is by blocking the signaling pathways which are involved in the regulation of oncogenesis. These molecular therapies have anti-angiogenic and anti-vascular properties that act against factors like VEGF and PDGF or against oncogenes like Ret and Kit which are primarily involved in the pathogenesis of a tumor formation.
(Le Tourneau C et al., 2008)
TK proteins participate in the proliferation, differentiation and apoptosis at the cellular level. TKIs are targeted molecules that are similar to ATP and competes with real ATP and binds to the tyrosine part of TK molecule. There by inhibiting the oncogenesis pathways.(Illouz F et al., 2009) There are various molecular targeted therapies which include Sunitinib, Imatinib, Sorafinib, Motesanib.
Previous studies have highlighted the development of thyroid dysfunction at an increased rate in patients who are treated with TKIs. (Torino F et al., 2009) The pathogenesis of thyroid dysfunction in patients who are on TKIs is explained by the development of thyroiditis,production of antithyroid peroxidase antibodies, capillary regression in the thyroid gland and by the reduced glandular uptake of iodine.(Mannavola D et al., 2007) (de Groot JW et al., 2006)
This study was designed to study the change in the biochemical values of thyroid profile among CML patients with Philadelphia chromosome positive status who were treated with TKIs.

2. MATERIAL AND METHODS

Institutional Ethics Committee approval was obtained prior to the commencement of the study. A retrospective observational study was conducted using the records of patients attending the hematology OPD of a tertiary care hospital in Tamilnadu. The CML patients who had Philadelphia chromosome positive status were enrolled for the study. Patients who were negative for Philadelphia chromosome or in blast crisis were excluded from our study Records of 100 patients who met the inclusion and exclusion criteria were screened and the data was recorded in a structured clinical record form. Reports of the thyroid profile (TSH, T3 and T4) done before and after the treatment with TKIs were collected. Statistical analysis was done using parametric test for continuous variables and statistical significance was for $P < 0.05$

3. RESULTS

Among the 100 patients in our study, 73% were males and 27% were females. 64% of the patients were in the age group of 41 to 60 years. The age sex distribution is shown in Fig. 1.

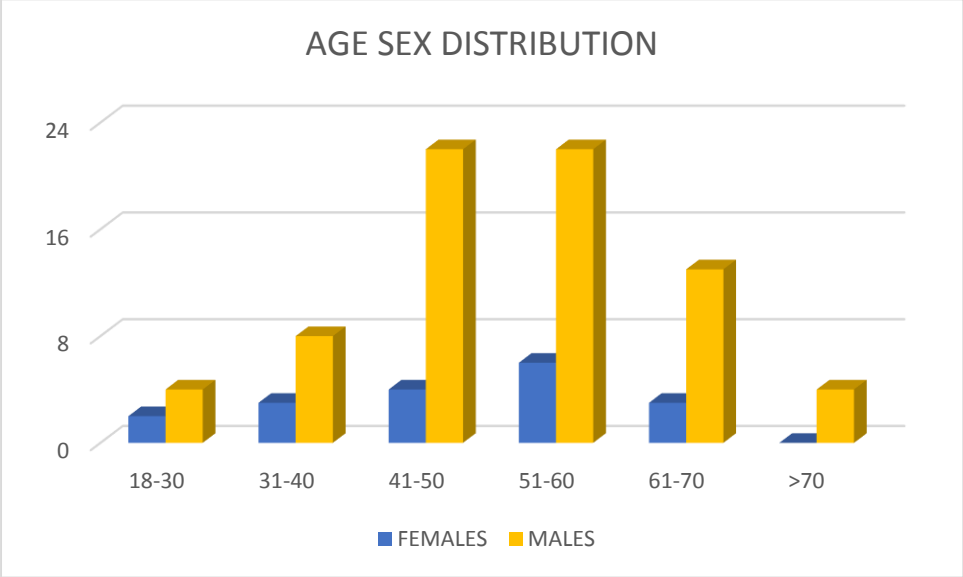

Fig. 1: Age Sex distribution of patients

Before the start of treatment with imatinib, 91% of patients with CML were euthyroid. At the end of treatment phase, among these euthyroid patients, a further 6 of them developed subclinical hypothyroidism as characterized by an elevation of the serum TSH between 5.5 and 10. {Figure 2}

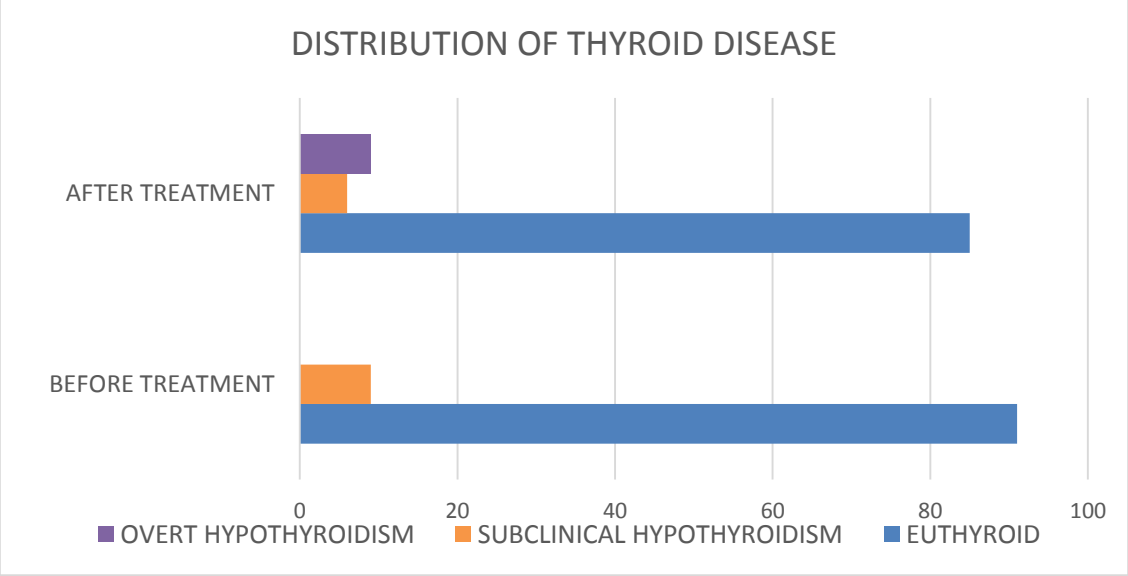

Fig. 2: Thyroid status of patients pre and post treatment

The comparison of the pre and post intervention values of the patients was done using paired student's t – test. The values are shown in Table 1. There was statistically significant raise in the serum TSH and fall in the T3 and T4 values after the completion of treatment of 6 months.

Table 1:
Serum levels of thyroid hormones and TSH pre and post treatment in CML patients

	BEFORE	AFTER	DIFF	95% CI	P value
TSH	3.33 ± 1.12	3.90 ± 1.49	- 0.573	-0.776 to -0.369	<0.00001
T3	117.79 ± 33.65	112.45 ± 32.08	5.34	3.35 to 7.33	<0.00001
T4	7.14 ± 1.80	6.68 ± 1.74	0.46	0.323 to 0.598	<0.00001

At the beginning of the study period, 9% of patients were having subclinical hypothyroidism while the remaining were euthyroid. At the end of 6-month treatment period, the 9% of patients had overt hypothyroidism while 6% of patients had subclinical hypothyroidism. The change in the presence of thyroid dysfunction was statistically significant (P = 0.0042) by Fisher's exact probability test. (Table 2)

Table 2:
Distribution of thyroid status pre and post treatment in CML patients

	EUTHYROID	SUBCLINICAL HYPOTHYROIDISM	OVERT HYPOTHYROIDISM
BEFORE TREATMENT	91	9	0
AFTER TREATMENT	85	6	9

4. DISCUSSION

The sex distribution was strongly in favor of males in our study which is somewhat similar to previous studies which showed a slight male predominance. (Williams Hematology., 2010) In a study from North Karnataka, India, the incidence of CML was maximum in 41 – 50 years age group which is similar to the findings in our study were the maximum patients were seen in the age group 0f 41 – 60 years. (Modak et al., 2011)

CML patients on TKIs develop thyroid abnormalities as an adverse event. They usually require higher dose of Levothyroxine in patients who were known hypothyroidism prior to treatment with TKIs. (Torino F et al., 2009)
Patients who were euthyroid prior to TKI therapy developed transient subclinical hypothyroidism and require follow up and treatment. (Surks MI et al., 2004)

In our study, before imatinib therapy, 9% showed subclinical hypothyroidism. After 6 months of post therapy, 9% developed overt hypothyroidism and 6% subclinical hypothyroidism. It clearly demonstrates that the patients had increased thyroid dysfunction post imatinib therapy. Thus it indicates the need to increase the dose of thyroxine in these patients.
Studies by Groot et al. found that TKI therapy does not cause thyroid abnormality in euthyroid whereas in patients with hypothyroidism had significant increase in TSH levels. (de Groot et al., 2005) (de Groot et al., 2007). Increase in levothyroxine dose is needed in these patient as imatinib causes enzyme induction by clearance of non deiodination.
Patients with intact thyroid glands remained euthyroid even while on imatinib therapy. In a study by Dora et al. found no adverse effect of imatinib on thyroid function. (Dora et al., 2008)
The pathogenesis of imatinib-induced subclinical or overt hypothyroidism was by stimulation of T3 and T4 clearance leading to increased activity of hepatic microsomal enzyme, uridine-diphosphate-glucuronyltransferase (UGTs) (de Groot et al., 2006)
In a study reported by Kim et al were 64 patients treated for CML showed hypothyroidism in 13%, 50%, and 22% of patients with imatinib, dasatinib, or nilotinib therapy, respectively. (Kim et al., 2010)

TKIs that are used in the treatment of non-hematological malignancies have also been reported to cause thyroid dysfunction (Fallahi P et al., 2014). Especially, sunitinib had shown higher incidence of hypothyroidism close to 60%. (Funakoshi T et al., 2013)

Results from our study indicates that imatinib used in the management of Ph chromosome positive CML patients demonstrate thyroid dysfunction both sub clinical and overt hypothyroidism.

5. CONCLUSION

The incidence of hypothyroidism in our study population was significant. The presence of thyroid profile abnormality makes it necessary to screen for thyroid profile in CML patients, before the start of tyrosine kinase inhibitors.
It is also equally vital to monitor the thyroid profile during the course of treatment and post therapy for detecting thyroid dysfunction.
In subclinical hypothyroid patients, regular follow up is recommended. Early diagnosis and treatment will improve the quality of life, survival and prognosis.
Discontinuation of TKIs due to hypothyroidism is not recommended. More studies must be encouraged in future to study the level of thyroid dysfunction in patients on tyrosine kinase inhibitors.
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Conflict of Interest – Nil

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