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# Tyrosine kinase inhibitors induced thyroid dysfunction: myth or reality?

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## ABSTRACT

**Background:** Chronic myelogenous leukemia (CML) is a hematopoietic stem cell disorder. It is associated with acquired genetic changes in the hematopoietic stem cells in the form of BCR-ABL fusion gene also known as Philadelphia chromosome.

**Materials and methods:** We prospectively studied thyroid function at baseline and at 6 months of imatinib treatment in 26 newly diagnosed BCR-ABL positive CML patients.

**Result:** The thyroid-stimulating hormone (TSH) levels increased significantly from baseline (3.20 ± 0.978 mIU/L *vs.* 3.724 ± 1.726 mIU/L, $p < 0.05$) after 6 months of treatment, 88.4% of the patients remained euthyroid. Only 2 patients had subclinical hypothyroidism, 1 had hypothyroidism after 6 months of tyrosine kinase inhibitors (TKI) therapy.

**Conclusion:** Imatinib did not have any significant effect on thyroid function in CML patients in this study.

**Key words:** CML; imatinib; TSH; FT3; FT4

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## Introduction

Chronic myelogenous leukemia (CML) is a hematopoietic stem cell disorder presenting with anemia, elevated blood granulocytosis and the presence of immature granulocytes, basophilia, frequently, thrombocytosis and spleen enlargement [1]. It is associated with acquired genetic changes in the hematopoietic stem cells in the form of BCR-ABL Fusion gene also known as Philadelphia chromosome, in which a portion of ABL (Abelson) gene translocates from chromosome 9 and fuses with the remaining part of BCR (breakpoint cluster region) gene.

The annual incidence of CML in India is reported to be 0.8 to 2.2 per 100,000 people [2]. Clinically, CML is biphasic or triphasic disease that is usually diagnosed in the initial "chronic", "indolent" or "stable" phase and then spontaneously evolves after some years into an advanced phase, and a later blast crisis phase. Majority of patients are diagnosed in the "chronic" phase of CML. Tyrosine kinase inhibitors introduced in the 2000s act by binding to the enzymatic receptor proteins which then block the ATP-binding site in tyrosine kinases involved in cell proliferation, metastasis, or angiogenesis and, consequently, inhibit signal transduction. Although their mechanism of action is the same, they differ from each other in the spectrum of targeted kinases, pharmacokinetics, and specific adverse events. The emergence of such therapy derived the CML treatment from the non-targeted therapy to the targeted one which resulted in increased survival of these patients.

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Imantinib mesylate was the first tyrosine kinase inhibitor (TKI) used in the treatment of CML. The International Randomized Study of Interferon and STI571 (IRIS) is considered a landmark clinical trial for CML treatment with TKIs. Imatinib selectively inhibits BCR-ABL competitively, as well as several other kinases, including stem cell factor receptor (KIT), platelet-derived growth factor receptor (PDGFR), and colony-stimulating factor receptor-1 (CSF-1R) [8]. Other TKIs, such as dasatinib, nilotinib, bosutinib have also been used in CML patients. TKIs are known to inhibit vascular endothelial growth factor receptors (VEGFRs) and their downstream targets and suppress endothelial proliferation. This could cause reduced vascularity to thyroid gland, an extremely vascular gland. The reduced blood flow could result in destructive thyroiditis, leading to a transient period of thyrotoxicosis followed by hypothyroidism. Many other hypotheses have been proposed such as toxic effects on thyrocytes, reduced TPO activity, impaired iodine uptake, or stimulation of thyroiditis.

Among these, the most accepted theory is that of anti-angiogenic effect of TKIs. 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. For patients treated with TKIs who do not receive thyroid hormone replacement, systematic monitoring of thyroid function is required, as the symptoms of thyroid disease can also be confused with treatment-related toxic effects, leading to alterations in treatment, or with other complications leading to misplaced treatment strategies and, ultimately, affecting patient's quality of life.

Some reports have found that development of thyroid dysfunction may be a marker for increased likelihood of response to therapy. Because thyroid disturbances induce adverse effects that complicate management of the patients with CML, it seems that the relation between the TKIs and thyroid disorders should be investigated.

## Materials and methods

This was an observational and longitudinal study, conducted at a tertiary care hospital in India from April 2021 to Jan 2022. For this purpose, all diagnosed patients of chronic myeloid leukemia coming to hospital OPD and IPD were enrolled after taking written and informed consent and were kept on follow up for 6 months to assess the presence of thyroid dysfunction after giving tyrosine kinase inhibitors therapy. Institutional Reference Intervals used were: thyroid-stimulationg hormone (TSH): euthyroid: 0.27–4.2 μIU/mL (mIU/L), hyperthyroid: < 0.27 μIU/mL (mIU/L) and hypothyroid: > 4.20 μIU/mL (mIU/L); free thyroxine (FT4): 1–1.7 ng/dL; free triiodothyronine (FT3): 2.7–4.3 pg/mL; anti-thyroid peroxidase antibodies (anti-TPO Ab): < 34 IU/mL.

Data thus obtained were analysed statistically. The data were presented by mean ± standard deviation for continuous variables and frequencies with their respective percentages were given for categorical variables. A p value <0.05 was considered as statistically significant.

## Results

As described above, a prospective study was done with 26 eligible patients with newly diagnosed CML. Out of the 26 patients, 14 (53.8%) were female and 12 (46.2%) were male. The mean age of the study populations was 39.65 years. The mean haemoglobin at presentation was 10.69 g%. The mean baseline characteristics of the patients are described in Table 1.

The mean TSH at presentation was 3.200 ± 0.978 uIU/mL (Fig. 1; Tab. 2). After 6month's therapy with tyrosine kinase inhibitors, a follow up analysis was done of the thyroid function tests. All the statistical variables were compared and a significant increase in the mean TSH levels was found after 6 months of tyrosine kinase inhibitors therapy. The mean TSH at 6 month follow up was 3.724 ± 1.726 IU/mL, with a p-value of < 0.05. During follow up, 2 patients (7.69%) developed sub clinical hypothyroidism with the presence of anti-TPO Ab, 1 patient developed hypothyroidism (3.8%) and, also, no significant changes were found in the levels of FT3, FT4, anti-TPO and anti-thyroglobulin antibodies (anti-TG Ab) level after the follow up (Fig. 2). Table 3 also shows age wise and gender wise distribution of the 7 patients who developed thyroid dysfunction. It also shows the individualized thyroid function tests 8 at baseline and at 6 months follow up in those three patients who developed thyroid dysfunction.

**Table 1.** Baseline parameters

| Variable | N (%)<br>Mean ± SD | Range (min.–max.) |
|---|---|---|
| **Sex**<br>Male<br>Female | <br>12 (46.2%<br>14 (53.8%) | |
| Age (Years) | 39.65 ± 15.46 | 8–76 |
| Hb (g%) | 10.69 ± 2.02 | 7.6–14.9 |
| TLC (/cumm) | 119,557.69 ± 106,137.75 | 2300–398,000 |
| Platelets (lakhs/cumm) | 2.74 ± 1.21 | 1.15–5.70 |
| Spleen size on USG Abdomen [cm] | 16.96 ± 3.21 | 12.0–24.0 |

Hb — hemoglobin; TLC — total leucocyte count; USG — ultrasonography; SD — standard deviation

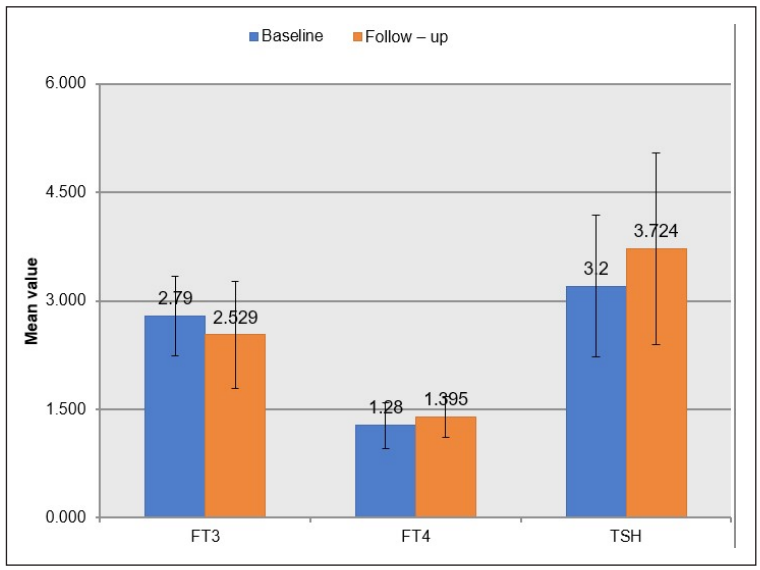


**Figure 1.** Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)

**Table 2.** Change in variables from baseline to follow-up

| Variable | Baseline | | Follow-up | | Change | | 't' value | p-value |
|---|---|---|---|---|---|---|---|---|
| | Mean | ± SD | Mean | ± SD | Mean | ± SD | | |
| FT3 | 2.793 | 0.549 | 2.529 | 0.736 | 0.264 | 0.823 | 1.637 | 0.114; NS |
| FT4 | 1.279 | 0.315 | 1.395 | 0.284 | 0.115 | 0.369 | 1.592 | 0.124; NS |
| TSH | 3.200 | 0.978 | 3.724 | 1.326 | 0.524 | 0.944 | 2.831 | 0.009* |
| Anti-TPO | 28.776 | 18.497 | 38.671 | 25.673 | 9.895 | 25.209 | 2.001 | 0.056; NS |
| Anti-TG | 34.141 | 21.469 | 37.546 | 15.317 | 3.405 | 22.436 | 0.774 | 0.446; NS |

Paired 't' test: NS; $p > 0.05$; Not significant; *$p < 0.05$; Significant. FT4 — free thyroxine; FT3 — free triiodothyronine; anti-TPO Ab — anti-thyroid peroxidase antibodies; anti-TG Ab— anti-thyroglobulin antibodies; SD — standard deviation

## Discussion

The present observational and longitudinal study was conducted with the aim of evaluating thyroid dysfunction after giving TKI therapy at 6 months follow up. Our study revealed a significant increase in S. TSH levels ($p < 0.05$) after a 6-month follow up period. These results are similar to a study by Khaleel et al. in which thirty-one patients with CML and 31 healthy controls were

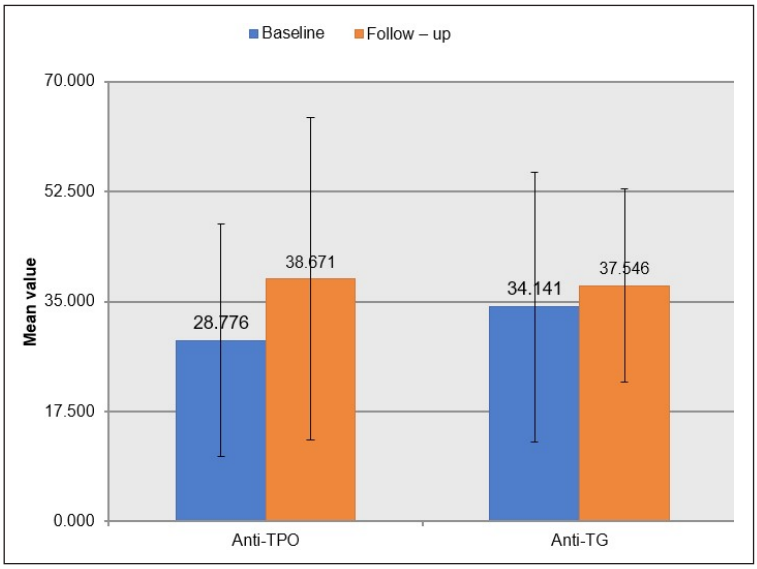


**Figure 2.** Anti-thyroid peroxidase antibodies (anti-TPO Ab), anti-thyroglobulin antibodies (anti-TG Ab)

**Table 3.** Thyroid function tests in patients who developed thyroid dysfunction

| S No. | Age [years] | Sex | FT3 [pg/ml] | FT4 [ng/dl] | TSH [µIU/mL] | FT3 [pg/ml] | FT4 [ng/dl] | TSH [µIU/mL] |
|---|---|---|---|---|---|---|---|---|
| 1 | 28 | Female | 2.37 | 1.22 | 3.89 | 2.72 | 0.43 | 9.7 |
| 2 | 24 | Female | 2.66 | 0.96 | 4.1 | 1.23 | 1.1 | 5.13 |
| 3 | 30 | Male | 3.8 | 2.1 | 3.93 | 0.86 | 1.6 | 5.32 |

Institutional reference range of thyroid function test in age group of 20–30 years. Free triiodothyronine (FT3) (pg/mL) — 2.32–6.09; free thyroxine (FT4) (ng/dL) — 0.78–2.19; thyroid-stimulating hormone (TSH) (µIU/mL) — 0.46–4.2

enrolled in a cross-sectional study. All the patients in the study group were on nilotinib for at least 6 months. The study showed 10% of the patients to have hypothyroidism and 3% to have hyperthyroid, while the rest (87%) were normal regarding thyroid function. There was a significant difference between the study and control group in thyroid stimulating hormone levels ($p < 0.05$) with the level being higher in the study group [9].

Similarly, in a study done by Masshadi et al., 16 newly diagnosed CML patients were enrolled. After 12 weeks of Imatinib therapy, there was a statistically significant decrease in TSH and statistically significant increase in T3 levels, 4 weeks after therapy. However, these alterations were not followed by any clinical manifestations of the same [18]. In a study, by Patel et al., 326 cases of thyroid dysfunction induced by TKIs were collected from Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and literature. Among those cases, 74% had hypothyroidism, 20% had hyperthyroidism, 6% had an unspecified type of thyroid dysfunction. This study also concludes the time taken for the development of thyroid dysfunction is quite varied, with 54% patients developing thyroid dysfunction within the first nine months of start of TKIs, with majority of cases requiring intervention with thyroid replacement or anti thyroid therapy [19].

## Conclusions

Based on the results of this study, there was a significant change in the serum TSH levels during TKI therapy, but all variables were within normal ranges. However, larger studies with larger sample sizes are recommended to prove TKI-induced thyroid dysfunction.

### Author contribution

All the authors participated in manuscript conception, patient data collection and interpretation, and writing and review of the manuscript. All authors had full access to all the data in the study

and take responsibility for integrity of the data and the accuracy of the data analysis. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors.

### Conflict of interest

None declared.

### Funding

None declared.

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