



Research Article

Imatinib and Thyroid Dysfunction in BCR-ABL Positive CML Patients

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Abstract

Background: Thyroid dysfunction is a known adverse effect of some tyrosine kinase inhibitors like sunitinib and sorafenib while imatinib has been shown to induce hypothyroidism and increased requirement of levothyroxine in thyroidectomized patients. Very few retrospective studies are available for CML patients treated with imatinib, which have demonstrated conflicting effects on thyroid function.

Experimental design: We have prospectively studied thyroid function at baseline and at 6 months of imatinib treatment in 30 newly diagnosed BCR-ABL positive CML patients.

Results: Two (6.7%) patients had subclinical hypothyroidism at diagnosis with the prevalence not being different from general population. Though the TSH levels increased significantly from baseline (3.80 ± 2.00 mIU/L vs. 3.14 ± 1.65 mIU/L, $p = 0.016$) after 6 months of treatment, 90% of the patients remained euthyroid. Only 3 patients had subclinical hypothyroidism.

Conclusion: Imatinib did not have any significant impact on thyroid function in CML patients but may possibly alter the peripheral metabolism of thyroid hormones.

Keywords: CML; Imatinib; TSH; FT3; FT4

Peer Reviewer: Mohamed Bouattour, MD, Department of Hepatology and Department of Medical Oncology, Hospital Beaujon, France; Hend Ahmed El-Hadaad, Department of Clinical Oncology and Nuclear Medicine, Mansoura University, Egypt

Received: April 9, 2013; **Accepted:** June 5, 2013; **Published:** August 8, 2013

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

CML

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by anaemia, extreme blood granulocytosis, granulocytic immaturity, basophilia, often thrombocytosis, and splenomegaly[1]. The hematopoietic cells contain the fusion gene BCR-ABL, which encodes a constitutively active tyrosine kinase responsible for the initiation and maintenance of the chronic phase of CML[2,3]. The natural history of the chronic phase of the disease is to undergo clonal evolution into an accelerated phase and/or a rapidly progressive phase (blast crisis) resembling acute leukemia in a median time of four years, which is refractory to therapy[4]. Imatinib mesylate is a small molecular analogue of ATP that functions through competitive inhibition at the ATP binding site of the ABL kinase in the inactive conformation, which leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction[1,5]. Imatinib induces apoptosis in cells expressing BCR-ABL[1]. The goal of imatinib therapy is to decrease the cells bearing the t(9;22) translocation (leukemic cells) to the lowest levels possible (BCR-ABL/ABL expression ratio <0.05% by 18 months of therapy), under which conditions normal (polyclonal) haematopoiesis is restored[1].

Besides BCR-ABL imatinib mesylate is known to potently inhibit the platelet derived growth factor receptor- α (PDGFR- α), PDGFR- β , c-Fms, Arg and c-kit (stem cell factor receptor) tyrosine kinases[6]. Action on these tyrosine kinases may be responsible for many of the documented side effects of imatinib and effects on multiple endocrine hormones as well[6]. The leukemic stem cells (quiescent Ph-chromosome-positive cells, CD34+Lin-) are insensitive to imatinib *in vitro*, thus at present it is advisable to maintain treatment indefinitely until the criteria for cessation, if any, can be established in clinical trials[1,7]. Effects of imatinib on multiple endocrine hormones are being recognized and may affect quality of life in the CML patients and cause compliance issues.

Tyrosine kinase inhibitors and thyroid dysfunction

Sunitinib and sorafenib are multitargeted tyrosine kinase inhibitors that have been demonstrated to induce hypothyroidism by multiple studies[8]. Retrospective studies indicate that sunitinib can induce hypothyroidism in 53-85% of patients, and in prospective studies this complication has been reported in 36-71% of patients[8-10]. Sorafenib has been reported to be responsible for hypothyroidism in 18% of patients with metastatic renal-cell carcinoma[11]. Due to similar mechanisms of action, it is possible that imatinib is also associated with thyroid dysfunction[8].

Kim *et al.* detected thyroid abnormalities in 25%, 55%, and 70% of Philadelphia chromosome positive CML patients under treatment with imatinib, nilotinib, and dasatinib respectively[12]. Dora *et al.*, reported normal TSH in 63 (92.6%) out of 68 CML patients on imatinib therapy, but elevated TSH (5.08-12.55 mU/L) in 5 (7.4%) patients[13].

Groot *et al.* described increased symptomatic requirement of levothyroxine and elevated TSH levels in previously thyroidectomized patients receiving imatinib for gastrointestinal stromal tumor or medullary thyroid carcinoma[14,15].

Although generally well tolerated, common side-effects of imatinib are fatigue and periorbital and peripheral oedema[1,4]. Symptoms of hypothyroidism are almost undistinguishable from these side-effects[14]. With the above background of conflicting reports and scarcity of prospective studies on the effect of imatinib on thyroid function in CML patients, we planned to study the thyroid function in CML patients on treatment with imatinib mesylate in comparison to the baseline levels.

Material & methods

Patient selection and study design

The present study was a prospective, observational and non-randomized study conducted on 30 newly diagnosed patients of CML in chronic phase. Patients

were enrolled from the Haematology Clinic at Pt. BD Sharma Post graduate Institute of Medical Sciences, Rohtak, Haryana after obtaining informed consent. The study was conducted over 18 month duration from June 2011 to December 2012. Diagnosis was confirmed by real time PCR for BCR-ABL fusion transcript. Imatinib was given initially in a dosage of 400 mg/day and increased to 600 mg/day or to 800 mg/day (400 mg every 12 hours), if required and tolerated [1]. Patients with other acute or chronic co-morbidities (liver and kidney diseases, other malignancies, endocrine disorders besides primary hypothyroidism, CML- accelerated phase or blast crisis, chronic infections like tuberculosis etc.) were excluded. CML – accelerated phase was defined as blood or marrow blasts between 10 and 20%, or blood or marrow basophils >20%, or platelet count <100 x 10⁹/L and blast crisis as blood or marrow blasts >20% [4]. Patients who used drugs with potential interference in thyroid function tests in the six months prior to the study entry or during follow up were also excluded. Haematological remission was defined as total leukocyte count <10 x 10⁹/L, platelet count <450 x 10⁹/L, no immature myeloid cells in the blood, disappearance of all signs and symptoms related to leukemia (including palpable splenomegaly) lasting for at least 4 weeks [1,5]. Thyroid function tests - TSH, free thyroxin, free tri-iodothyronine and anti - thyroid peroxidase antibody, (anti-TPO Ab) for patients with elevated TSH, and clinical assessment (for thyroid abnormalities) were done at the time of diagnosis (baseline). Patients were reassessed for thyroid dysfunction after 6 months of imatinib therapy. Ethical approval was taken from the institutional board of studies.

Thyroid function tests

Fasting early morning venous blood sample was taken in a plain red capped evacuated blood collection tube under all aseptic precautions for TSH, free thyroxin (FT4) and free tri-iodothyronine (FT3) estimation by chemiluminisence technique on ADVIA Centaur system (Siemens) [16]. Anti-TPO Ab was estimated

using chemiluminisence techniques on Immulite system (Siemens) [16]. Appropriate external quality controls were also run.

Institutional Reference Intervals used were:

TSH: euthyroid: 0.35 - 5.50 μ IU/mL (mIU/L),
hyperthyroid: < 0.35 μ IU/mL (mIU/L)
and hypothyroid: > 5.50 μ IU/mL (mIU/L).

FT4: 0.89 - 1.76 ng/dL,

FT3: 2.3 to 4.2 pg/mL,

Anti-TPO Ab: < 35 IU/mL

Subclinical primary hypothyroidism was defined by a serum TSH above the upper reference limit in combination with a normal free thyroxine (T4). Overt primary hypothyroidism was defined by a serum TSH above the upper reference limit in combination with low free thyroxine (T4) [17,18]. Treatment was recommended for patients with overt primary hypothyroidism and for patients with subclinical hypothyroidism with elevated Anti-TPO Ab or TSH > 10 μ IU/mL [17].

The data was compiled and subject to statistical analysis using SPSS v20. Baseline and post therapy values were compared using Wilcoxon sign test. Paired proportions were compared by McNemar's test.

Observations

Patient characteristics: In the present study there were 17 (56.7%) male and 13 (43.3%) female patients (1.3:1). Median age at diagnosis was 38.5 years. All the patients presented in chronic phase of CML. Median haemoglobin levels were 8.5 g/dL and median total leucocyte count was 75 X 10⁹/L at presentation. Patients had a median of 5.0% blasts in peripheral blood at diagnosis. Median platelet count was 300 X 10⁹/L. Median duration of symptoms in the patients was 6 weeks. Three out of 30 patients were asymptomatic and diagnosed incidentally on routine lab examination.

Treatment outcomes: 26 patients (87.7%) achieved haematological remission at 6 months of imatinib therapy while 4 (13.3%) patients were not in remission. Imatinib dosage was increased to 600 mg/day in 2 patients and to 800 mg/day in 4 patients. 6 (20%) patients had peripheral edema on legs, 4 (13.3%) had periorbital edema, 6 (20%) had fatigue, 5 (16.6%) had myalgia, 6 (20%) had cutaneous reactions (rashes) and 2 (6.6%) patients had complaints of cough as adverse effects of imatinib.

Thyroid function tests (TSH, FT4 AND FT3) at baseline: At diagnosis median serum TSH levels were 2.95 mIU/L, FT4 levels were 1.40 ng/dL and serum FT3 levels were 2.60 pg/mL (Table 1). Two (6.7%) patients had TSH >5.5 mIU/L and normal FT4 and FT3 (subclinical hypothyroidism). Both were not receiving any levothyroxine replacement as TPO (thyroid peroxidase) antibody levels were within reference range and TSH was < 10 mIU/L.

Table 1 Comparison of TSH, FT4 & FT3 levels in CML patients and after therapy (M=17, F = 13)

		BASELINE	6 MONTHS	p value
TSH (mIU/L)	Mean	3.14 ± 1.65	3.80 ± 2.00	0.016
	Median	2.95	3.75	
	Range	0.40 - 7.50	0.80 - 9.60	
FT4 (ng/dL)	Mean	1.50 ± 0.60	1.42 ± 0.55	0.173
	Median	1.40	1.33	
	Range	1.10 - 4.50	0.90 - 4.10	
FT3 (pg/mL)	Mean	2.55 ± 0.45	2.71 ± 0.52	0.136
	Median	2.60	2.72	
	Range	1.80 - 4.0	1.90 - 3.87	

Thyroid status after 6 months of imatinib therapy: Serum TSH levels increased significantly after 6 months of imatinib therapy (3.80 ± 2.00 mIU/L vs. 3.14 ± 1.65 mIU/L, $p=0.016$), though the median level (3.75 mIU/mL) was in euthyroid range (Table 1 & Fig. 1). 90% patients had euthyroid TSH levels. 3 patients (10%) had abnormal TSH (>5.5 mIU/L) after 6 months of imatinib therapy. All three had normal FT3 and FT4 (subclinical hypothyroidism). Two of these patients had baseline subclinical hypothyroidism as well. TSH levels worsened (9.6 mIU/L from baseline 7.5 mIU/L

and 7.6 mIU/L from baseline 5.8 mIU/L) from baseline in both. In the remaining one patient TSH levels worsened from baseline euthyroid levels (baseline TSH 3.7 mIU/L, post therapy 6.7 mIU/L). All the three patients had TPO levels within reference range and TSH < 10 mIU/L. They were not given any treatment for thyroid dysfunction. Fatigue, periorbital and peripheral edema was present in all three patients. There were no other clinical manifestations associated with thyroid dysfunction.

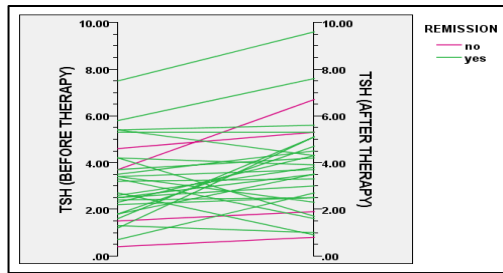


Fig. 1 Comparison of S. TSH before and after IMATINIB therapy in CML patients

Serum FT4 levels were 1.42 ± 0.55 ng/dL after 6 months of imatinib therapy as compared to 1.50 ± 0.60 ng/dL ($p = 0.173$). Serum FT3 levels were 2.71 ± 0.52 pg/mL after 6 months of imatinib therapy as compared to baseline levels of 2.55 ± 0.45 pg/mL ($p = 0.136$) (Table 1 & Fig. 1-3). All levels were in euthyroid range.

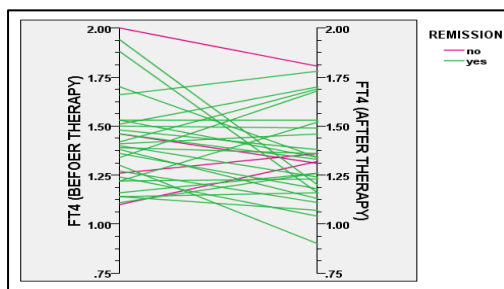


Fig. 2 Comparison of FT4 before and after IMATINIB therapy in CML patients

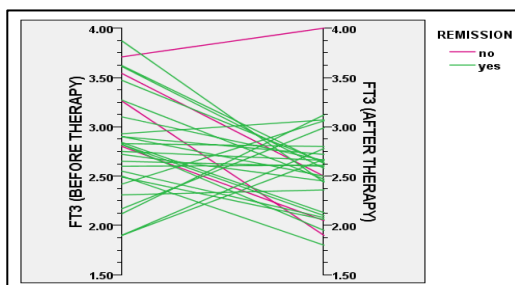


Fig. 3 Comparison of S. FT3 before and after IMATINIB therapy in CML patients

Discussion

In the present study male: female ratio was 1.3:1. In general, the male predominance has been estimated to

be 1.3-1.4:1[1,4]. Median age at diagnosis was 38.5 years (15-60 years). Though the incidence of CML has been known to increase logarithmically with age, Dikshit *et al.* noted the peak age in younger population in hospital based data than the 55-74 years described in population based studies[19]. Modak *et al.* also described the highest incidence in 36-45 years age group[20]. We observed a remission rate of 87.7%. The hematologic remission rate of patients treated with imatinib has been reported to be 95%[1].

The prevalence of thyroid abnormalities at baseline (6.7%) was similar to the prevalence in general population. Patricia *et al.* has reported a prevalence of 6.6% for thyroid disorders in general population[21]. Menon *et al.* reported a prevalence of 12.2% for goiter in adult population of an iodine sufficient region in India[22]. Abraham *et al.* reported a prevalence of 15.8% for thyroid abnormalities (mostly subclinical hypothyroidism in women in south India[23]. Kim *et al.* and Dora *et al.* also described normal baseline thyroid function in most CML patients and that the prevalence of thyroid abnormalities was not more than the prevalence in general population[12,13]. CML itself was not found to have any impact on thyroid function by Földes *et al.*, who observed that apart from a few cases, there was no dysfunction of the pituitary thyroid axis in interferon- γ treated CML patients in the remission phase[24].

While TSH levels significantly increased from baseline levels, only one patient developed subclinical hypothyroidism from previous euthyroid state. TSH levels worsened in the two cases of subclinical hypothyroidism. 90% of patients remained euthyroid after 6 months of treatment with imatinib. Imatinib therapy did not have any significant impact on thyroid status. The findings of the present prospective study are consistent with those described by Dora *et al.*, who observed that out of 68 patients of CML on imatinib treatment studied, serum TSH was in the normal range of 63 out of 68 (92.6%) but slightly elevated in 5 (7.4%) patients (5.08-12.55 mU/L). All subjects displayed levels of T4, FT4, and T3 in the normal

range. The serum TSH levels before and after imatinib therapy, available only for a subgroup of ten patients, were comparable (2.39, 1.82-3.05 mIU/L vs 2.71, 1.71-3.25 mIU/L) in their study [13].

In the study by Kim *et al.* only 8 patients were on imatinib therapy. While one had hypothyroidism both at baseline and after imatinib therapy, one developed subclinical hyperthyroidism following therapy [12].

Groot *et al.* reported that there was increased symptomatic requirement of levothyroxine and elevated TSH whenever imatinib was used in an elderly thyroidectomized patient for metastatic gastrointestinal stromal tumour [14]. In another study on eleven patients (1 with gastrointestinal stromal tumor and 10 with medullary thyroid carcinoma) treated with imatinib, Groot *et al.* observed hypothyroid features and increased dosage of levothyroxine replacement in all patients who had previously undergone thyroidectomy, whereas patients with the thyroid *in situ* remained clinically and biochemically euthyroid. They reported that TSH levels increased to 384±228% of the upper limit in patients having thyroidectomy and that imatinib associated complications led to the discontinuation of therapy in 36% of patients [15]. The increased demand for levothyroxine induced by imatinib in patients under levothyroxine replacement might indicate increased peripheral metabolism of thyroid hormones. Induction of hepatic conjugation with glucuronates and sulphates has been proposed [12,13]. Another potential explanation could be increased hormonal deiodination to reverse T3 through enhanced deiodinase type 3 (D3) activity [12,13].

Increased peripheral metabolism of thyroid hormones may also be responsible for the increase of TSH from baseline levels in both euthyroid and subclinical hypothyroid subjects in the present study. A normally functioning hypothalamic-pituitary-thyroid axis compensates for the possibly altered peripheral thyroid hormone metabolism.

The limitations of present study include absence of a

healthy control group, small sample size and infrequent follow up to compare duration of therapy in patients with and without thyroid dysfunction. Further studies in larger number of patients with frequent and prolonged follow up are recommended.

Conclusions

Thus we conclude that the thyroid function tests are largely unaltered after six months of imatinib therapy in CML patients. But the increased TSH suggests possible alterations in the peripheral metabolism of thyroid hormones.

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