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

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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.

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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...
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 and evaluated imatinib-induced thyroid abnormalities in 6-month duration by Ghalaut et al. In this prospective study, imatinib was reported in 25% of patients during therapy courses even for previously euthyroid patients. 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-glucuronyltranserase (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...
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.

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Conflict of Interest
The authors declare no conflict of interest.