Thyroid dysfunction in chronic myeloid leukemia patients on nilotinib

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Abstract:
BACKGROUND: The use of tyrosine kinase inhibitors has dramatically improved the prognosis of chronic myeloid leukemia (CML). Nilotinib has been reported to be associated with hypothyroidism and hyperthyroidism.

OBJECTIVES: The current study aims to evaluate the prevalence of thyroid dysfunction in a sample of Iraqi patients with CML (chronic phase) treated with nilotinib and its possible association with grade of other hematological parameters.

PATIENTS AND METHODS: Thirty-one patients with CML and the same number of healthy controls were enrolled in this cross-sectional study. All the patients were on nilotinib hydrochloride for at least 6 months.

RESULTS: Approximately 10% of the patients were having hypothyroidism and 3% were 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.

CONCLUSION: Thyroid dysfunction, particularly hypothyroidism is a clinically important adverse effect of nilotinib. Monitoring of thyroid function is required for patients taking this drug.

Keywords: Chronic myeloid leukemia, nilotinib, thyroid dysfunction, tyrosine kinase inhibitor

Introduction

Chronic myeloid leukemia (CML) which is usually abbreviated as CML is a chronic myeloproliferative neoplasm that accounts for about 15% of leukemia cases in the adults.\(^1\) CML has received the attention for being a paradigm for understanding the molecular bases of cancer. The disease results from a translocation which involves the ABL and BCR gene on chromosome 9 and chromosome 22, respectively.\(^2\) The translocation will result in a fusion gene termed BCR-ABL or the Philadelphia chromosome that codes for a protein with excess tyrosine kinase activity.\(^3\) The disease can pass into three distinct phases: The chronic phase (CP) followed by the accelerated phase and finally the blast phase. Most of the patients are commonly diagnosed in the CP.\(^4\)

About two decades ago CML was treated using conventional nonspecific agents such as hydroxyurea, and interferon alfa and although \( \alpha \)-interferon improved the patients’ survival that effect was counteracted by its toxicity.\(^5\) Tyrosine kinase inhibitors (TKIs) can efficiently inhibit the association of adenosine triphosphate (ATP) with BCR-ABL1 protein. This process has the effect of halting the malignant clone proliferative expansion. The emergence of such therapy derived the CML treatment from the nontargeted therapy to the targeted one which resulted in increased survival of these patients.\(^6\)

Imatinib, dasatinib, and nilotinib are used commercially for the treatment of CML.
According to the present guidelines, they can be used as a frontline drug for the treatment of CML in the CP.[7]

Nilotinib is a second generation TKI. It is an analog to imatinib with higher affinity for the ATP binding sites in vitro[8] it can be used as a frontline drug for CML treatment and also for imatinib-resistant cases.

The inhibition of TKIs in other body tissues accounts for many side effects of these drugs. Several metabolic effects have been demonstrated with the use of nilotinib including hyperglycemia[9] and hypercholesterolemia.[10]

Thyroid abnormalities were also detected in patients using TKI so that frequent monitoring of thyroid function is required for the detection of thyroid dysfunction.[11]

Nilotinib was reported to be associated with hypothyroidism and to a lesser extent with hyperthyroidism in one study.[12] Other TKIs (sunitinib and dasatinib) have been reported to induce hypothyroidism with much higher frequency.[13]

Many different mechanisms have been postulated to explain the effect of TKI on thyroid function. One possible explanation is that nilotinib and other TKI will cause a state of capillary dysfunction through inhibition of vascular endothelial growth factor receptor. Capillary, dysfunction may be followed by glandular dysfunction with or without the development of thyroid autoantibodies.[14] Another possible mechanism is that TKI can lead to negative effect on the biosynthesis of thyroid hormone through inhibition of thyroperoxidase activity or inhibition of iodine uptake.[15]

The current study aims to evaluate the prevalence of thyroid dysfunction in a sample of Iraqi patients with CML (CP) treated with nilotinib and its possible association with other hematological parameters.

Patients and Methods

Thirty-three patients were enrolled in this cross-sectional study, 19 females and 14 males with an age ranging from 30 to 70 years. The study was done at the national center for hematological diseases in Baghdad-Iraq from February 2016 to October 2016. Patients included were diagnosed as CML based on peripheral blood findings and molecular analysis for the BCR-ABL mutation by polymerase chain reaction. Patients were on nilotinib hydrochloride (Tasigna, Novartis) 400 mg/d for 6 months. Switching to nilotinib treatment was due to intolerance or resistance to imatinib. Patients with a history of thyroid disease or are already on treatment for thyroid dysfunction were excluded from the study. Other exclusion criteria include: pregnancy, concomitant use of oral contraceptive pills or corticosteroids. All patients taking nilotinib who were attending the national center for hematological diseases were selected to be enrolled in this study who were fulfilling the inclusion criteria and devoid of the exclusion criteria explained earlier. The study also included a control group of 31 sex- and age-matched healthy individuals. Informed consent was taken from the patients, and the control group and all the procedures were approved by the Local Ethics Committee.

Serum thyroid stimulating hormone (TSH), total T3 and T4 were measured by a competitive enzyme immunoassay test (TOSOH, Japan). Serum samples were collected, processed, and analyzed according to manufacture manual. Laboratory reference ranges are 0.4–4 μU/ml for TSH, 70–170 ng/dl for T3 and 4.5–12.5 μg/dl for T4. Hematological parameters were measured using auto hematology analyzer (Mindray BC 3000, China).

Patients on nilotinib were classified according to common terminology criteria for adverse events (CTCAE) regarding hemoglobin (Hb), platelets, and absolute neutrophil count (ANC).[16]

Statistical analysis

All results are expressed as mean ±SD. SPSS statistical programme version 21, IBM Corporation, Armonk, New York, United States. Prism 6.01, GraphPad Software, Inc. La Jolla, CA 92037 USA, has been used for data analysis and graphs development. T-test and chi-square statistical tests were used wherever appropriate. Sample size was estimated using PASS 12 software, Kaysville, Utah 84037 USA.

Results

Of the 33 patients who were taking nilotinib, 14 (42%) were males with mean age of 56 years and 19 (58%) were females with mean age of 52 years. The overall age mean was 53.9 years (range 30–70). The overall mean of ANC, Hb, and platelets were 4.2 × 10⁹/L, 12.5 g/dL and 191.9 × 10⁹/L, respectively.

Regarding the thyroid function test, both T3 and T4 overall means were within the normal range (96.1, 7.4), respectively. Furthermore, the minimum and the maximum values of both T3 and T4 were within the normal limits as can be shown in Table 1. TSH overall mean was within the normal values but both the minimum and the maximum values were not within the normal limits.

Approximately 10% of the patients were having hypothyroidism and 3% were hyperthyroid while the rest (87%) were normal according to the thyroid function.
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Iraqi Journal of Hematology - Volume 7, Issue 1, January-June 2018

Figure 1: Percentage of patients on nilotinib according to their thyroid status

Table 1: Patients parameters including sex, age, hematological values and thyroid function

| Patient characteristic         | Value       |
|-------------------------------|-------------|
| n                             | 33          |
| Male (%)                      | 1442        |
| Female (%)                    | 1958        |
| Age Mean±SD                   | 53.9±11.7   |
| Range                         | 30-70       |
| ANC (×10^9/L) Mean±SD         | 4.2±2.7     |
| Range                         | 0.9-16.15   |
| HB (g/dl) Mean±SD             | 12.5±1.19   |
| Range                         | 10.7-15.8   |
| Platelets (×10^9/L) Mean±SD   | 191.9±100.8 |
| Range                         | 62-518      |
| TSH (μU/ml) Mean±SD           | 2.3±1.8     |
| Range                         | 0.31-9.4    |
| T3 (ng/dl) Mean±SD            | 96.1±11.9   |
| Range                         | 78-140      |
| T4 (μg/dl) Mean±SD            | 7.37±1.7    |
| Range                         | 4.50-11.20  |
| Normal thyroid (%)            | 27(87%)     |
| Hypothyroid (%)               | 3(10%)      |
| Hyperthyroid (%)              | 1(3%)       |

ANC=Absolute neutrophil count, SD=Standard deviation, TSH=Thyroid-stimulating hormone, T3=Triiodothyronine, T4=Thyroxine, HB=Hemoglobin

Patients on nilotinib were classified according to CTCAE regarding Hb, platelets, and ANC levels as shown in Figure 2.

It is obviously shown that most of the patients had a normal Hb, platelets, and ANC levels (72%, 72%, and 83%, respectively). Only 27.3% of the patients had Grade 1 anemia. Grade (1, 2) neutropenia and thrombocytopenia were also observed among the patients.

All patients who were hypothyroid or hyperthyroid had a normal Hb and ANC levels, and only one patient with hypothyroidism had Grade 1 thrombocytopenia.

A comparison between patients with normal and hypothyroidism regarding age, Hb, platelets, and ANC revealed no significant difference between the two groups as shown in Table 2 with P > 0.05.

TSH, T3 and T4 values were compared between the study group of patients taking nilotinib and a control group of subjects who were not taking that drug. As shown in Table 3, there was a significant difference between the study and control group in TSH levels (P < 0.05) with the level being higher in the study group. On the other hand, no significant difference was noticed regarding T3 or T4 level between the two groups.

**Discussion**

The use of TKIs has changed dramatically the prognosis of CML in terms of response rate and overall survival. Despite this overwhelming success, many patients have been reported to suffer a variety of adverse effects affecting the thyroid function among other endocrine and various systems as well. The fact that tyrosine kinase is crucial for many functions in many tissues in addition to the nonselective nature of many TKIs has contributed substantially for the occurrence of these disturbing effects.

Nilotinib is a second generation TKI with many advantages over imatinib including its effectiveness in treating CML patients with imatinib resistance or intolerance as well as its superiorit over imatinib as front-line drug for the treatment of newly diagnosed CML.

In the present study, the prevalence of subclinical hypothyroidism was 10% of the total patients with CML in the CP who were on nilotinib for at least 6 months. None of the patients had symptomatic hypothyroidism. Comparing these results to the well-distinguished comprehensive study on the effect of TKIs on thyroid function where the prevalence of subclinical hypothyroidism in CML patients taking nilotinib who were also in the CP and whom were followed for 6-month period was about 15%. It is obvious that the results are comparable regarding the hypothyroidism and the higher percentage in the other study might be attributed to the larger sample size and the longer period of follow-up. The study was similar to the study done by Kim et al. regarding the observation that...
Table 2: Comparison of age, absolute neutrophil count, platelets, and hemoglobin between the normal and hypothyroid groups with t-test results

|                      | Mean±SD  | t-test |
|----------------------|----------|--------|
| Age                  |          |        |
| Normal thyroid       | 52.89±12.24 | P>0.05 |
| Hypothyroid          | 62.67±6.81  |        |
| ANC                  |          |        |
| Normal thyroid       | 4.29±2.98 | P>0.05 |
| Hypothyroid          | 3.23±0.49  |        |
| Platelets            |          |        |
| Normal thyroid       | 228.59±213.19 | P>0.05 |
| Hypothyroid          | 155.67±38.50 |        |
| Hemoglobin           |          |        |
| Normal thyroid       | 12.60±1.28 | P>0.05 |
| Hypothyroid          | 12.03±0.06  |        |

ANC=Absolute neutrophil count, SD=Standard deviation

There was no significant association between the state of thyroid dysfunction and the other hematological parameters (Hb, platelets, and ANC) as demonstrated in the result section and the majority of the patients regardless their thyroid function status were within the normal range of aforementioned hematological parameters according to CTCAE classification.

Thyroid dysfunctions particularly hypothyroidism have been reported frequently with other TKIs used in the treatment of CML. Patients taking imatinib who were already on thyroid replacement therapy reported an increase in thyroxine requirement,[21] while patients with euthyroid did not develop thyroid dysfunction.[22] Dasatinib is a second-generation TKI used in the treatment of imatinib-resistant Ph-positive CML. In one study,[12] 50% of the patients taking this drug developed hypothyroidism although these results have to be taken cautiously due to the very small sample size (only 10 patients). Many other TKIs that are used for nonhematological malignancies have been also shown to induce thyroid dysfunction[13] of which sunitinib is particularly worthy to mention due to the high incidence of hypothyroidism of about 60% with 27% of them requiring treatment.[23,24]

To the best of our knowledge, only one study done with acceptable sample size of about 60 patients to investigate none of the patients had developed clinical symptoms of hypothyroidism. In our study, only 3% of the patients had abnormal thyroid function tests (TFT) results consistent with hyperthyroidism. This is in contrast to the study done by Kim et al. where about 25% of patients developed that abnormality. Again the larger sample size and the longer period of follow-up are important factors to be considered, but other factors might play a part like the difference in the populations of patients sampled (Iraqi-middle East vs. German).
the thyroid dysfunction induced by nilotinib.\[22\] Not only used as a second-line treatment for imatinib-resistant CML patients, nilotinib is prescribed as frontline drug in the treatment of CP of CML according to the current guidelines.\[13\] Another aspect to be considered is the clinical implications of TKIs associated thyroid dysfunction. It has been reported that at least for some solid tumors that this side effect may have some prognostic value\[23,26\] which is an area that would be interestingly to be investigated in CML. Regarding the level of TSH that mandates replacement therapy, the American Association of Clinical Endocrinologists and the endocrine society recommends thyroid hormone to be initiated when TSH rises to a level above 10 µU/ml.

**Conclusion**

This study showed that a comprehensive knowledge about the side effects of this expanding used drug is substantial. This study demonstrated the prevalence of thyroid dysfunction in a sample of nilotinib prescribed Iraqi CML patient in comparison to other studies of different populations, and it is the second study after Kim et al. regarding the sample size. This study gives an overview of thyroid dysfunction in patients taking nilotinib and further studies with larger sample size investigating the impact of TFT on prognosis in CML patients is strongly recommended.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
2. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and giemsa staining. Nature 1973;243:290-3.
3. Bedi A, Zehnbauer BA, Barber JP, Shankis SJ, Jones RJ. Inhibition of apoptosis by BCR-ABL in chronic myeloid leukemia. Blood 1994;83:2038-44.
4. Sessions J. Chronic myeloid leukemia in 2007. J Manag Care Pharm 2007;13:4-7.
5. Silver RT, Woolf SH, Huhmann R, Appelbaum FR, Anderson J, Bennett C, et al. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: Developed for the American Society of Hematology. Blood 1999;94:1517-36.
6. Deininger M, O’Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, et al. International Randomized study of interferon vs. STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. Blood 2009;114:1126.
7. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2016 update on diagnosis, therapy, and monitoring. Am J Hematol 2016;91:252-65.
8. Weisberg E, Manley PW, Breitenstein W, Brüggen J, Cowan-Jacob SW, Ray A, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005;7:129-41.
9. Breccia M, Muscaritoli M, Gentilini F, Latagliata R, Carmosino I, Rossi Fanelli F, et al. Impaired fasting glucose level as metabolic side effect of nilotinib in non-diabetic chronic myeloid leukemia patients resistant to imatinib. Leuk Res 2007;31:1770-2.
10. Hiwase DK, Carne L, Ross D, Grigg A, Hughes TP. Hypercholesterolemia in imatinib intolerant/resistant CML-CP patients treated with nilotinib: A retrospective analysis. Blood 2013;122:1503.
11. Breccia M, Molica M, Alimena G. How tyrosine kinase inhibitors impair metabolism and endocrine system function: A systematic updated review. Leuk Res 2014;38:1392-8.
12. Kim TD, Schwarz M, Mogai H, Grillo P, Westermann J, Ploëckinger U, et al. Thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Philadelphia chromosome-positive chronic myeloid leukemia. Thyroid 2010;20:1209-14.
13. Fallahi P, Ferrari SM, Vita R, Di Domenicantonio A, Corrado A, Benvenga S, et al. Thyroid dysfunctions induced by tyrosine kinase inhibitors. Expert Opin Drug Saf 2014;13:723-33.
14. Makita N, Miyakawa M, Fujita T, Iiri T. Sunitinib induces hypothryroidism with a markedly reduced vascularity. Thyroid 2010;20:323-6.
15. Mannavola D, Coco P, Vannucchi G, Bertuelli R, Carletto M, Casali PG, et al. A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. J Clin Endocrinol Metab 2007;92:3531-4.
16. Trott A, Colesas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCFAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176-81.
17. O’Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
18. Shu M, Zai X, Zhang B, Wang R, Lin Z. Hypothyroidism side effect in patients treated with sunitinib or sorafenib: Clinical and structural analyses. PLoS One 2016;11:e0147048.
19. Kantarjian H, Giles F, Wunderle L, Bhalla K, O’Brien S, Wassmann B, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 2006;354:2542-51.
20. Hochhaus A, Rosti G, Cross NC, Steegmann JL, le Couture P, Ossenkoppele G, et al. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: Results from the European
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ENEST1st study. Leukemia 2016;30:57-64.

21. de Groot JW, Zonnenberg BA, van Ufford-Mannesse PQ, de Vries MM, Links TP, Lips CJ, et al. A phase II trial of imatinib therapy for metastatic medullary thyroid carcinoma. J Clin Endocrinol Metab 2007;92:3466-9.

22. de Groot JW, Zonnenberg BA, Plukker JT, van Der Graaf WT, Links TP. Imatinib induces hypothyroidism in patients receiving levothyroxine. Clin Pharmacol Ther 2005;78:433-8.

23. Wolter P, Stefan C, Decallonne B, Dumez H, Bex M, Carmeliet P, et al. The clinical implications of sunitinib-induced hypothyroidism: A prospective evaluation. Br J Cancer 2008;99:448-54.

24. Funakoshi T, Shimada YJ. Risk of hypothyroidism in patients with cancer treated with sunitinib: A systematic review and meta-analysis. Acta Oncol 2013;52:691-702.

25. Wolter P, Stefan C, Decallonne B, Dumez H, Fieuws S, Wildiers H, et al. Evaluation of Thyroid Dysfunction as a Candidate Surrogate Marker for Efficacy of Sunitinib in Patients (pts) with Advanced Renal Cell Cancer (RCC). Vol. 26. In: ASCO Annual Meeting Proceedings; 2008. p. 5126.

26. Shinohara N, Takahashi M, Kamishima T, Ikushima H, Sazawa A, Kanayama H, et al. Efficacy and Thyroidal Effects of Sunitinib in Japanese Patients with Metastatic Renal Cell Carcinoma: Hypothyroidism and Thyroid Atrophy as Potential Biomarkers for Sunitinib? Vol. 27. In: ASCO Annual Meeting Proceedings; 2009. p. E16097.