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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 α-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.

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According to the present guidelines, they can be used as a frontline drugs 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 less 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 T_3 and 4.5–12.5 μg/dl for T_4. 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 4.2×10^9/L, 12.5 g/dL and 191.9×10^9/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

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

test findings. None of the patients showed any clinical sign of hypothyroidism or hyperthyroidism Figure 1.

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

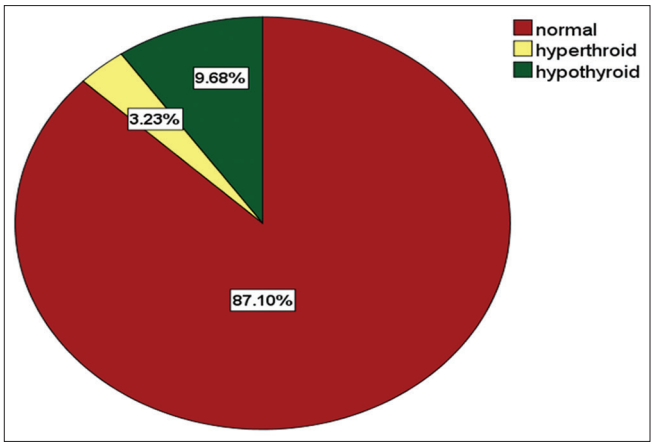

Figure 1: Percentage of patients on nilotinib according to their thyroid status

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.[17] Despite this overwhelming success, many patients have been reported to suffer a variety of adverse effects affecting the thyroid function[18] among other endocrine[11] 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[19] as well as its superiority over imatinib as front-line drug for the treatment of newly diagnosed CML.[20]

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,[12] 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*.[12] regarding the observation that

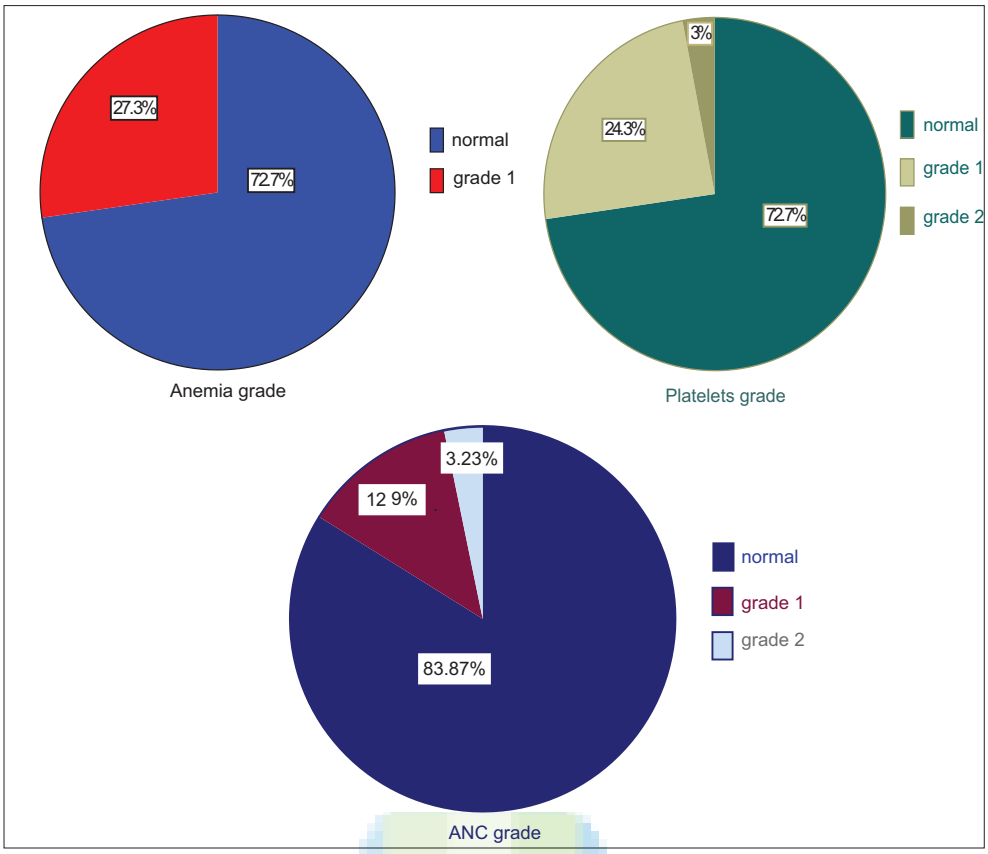

Figure 2: Patients classified according to common terminology criteria for adverse events regarding hemoglobin, platelets and absolute neutrophil count levels

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

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).

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 dysfunctionl.[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

Table 3: Comparison of thyroid-stimulating hormone, triiodothyronin and thyroxine between the study group (nilotinib) and control group (no nilotinib)

	Mean±SD	*t*-test
TSH		
Control	1.45±0.49	*P*<0.05*
Study	2.31±1.84	
T4		
Control	7.12±1.27	NS
Study	7.38±1.71	
T3		
Control	100.65±16.47	NS
Study	96.06±11.93	

TSH=Thyroid-stimulating hormone, T3=Triiodothyronine, T4=Thyroxine, SD=Standard deviation, NS=Not significant, *Significant

the thyroid dysfunction induced by nilotinib.[12] 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.[7] 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[25,26] 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.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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