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RESEARCH ARTICLE

THE IMPACT OF TYROSINE KINASE INHIBITORS ON THYROID FUNCTION TESTS AMONG SUDANESEPATIENTS WITH CHRONIC MYELOID LEUKEMIA

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ABSTRACT

Chronic myeloid leukemia used to think as an old type of leukemia, but nowadays any age can get it, it has many reasons but all lead to colonial proliferation of white blood cells (granulocyte mainly) with translocation between chromosome 9 and 22 giving rise a new one called Philadelphia chromosome, which is responsible for abnormal proliferation of myeloid cells. In Khartoum state, an oncology and nuclear medicine hospital is considered as a main treatment center for all kinds of cancer. Ethical approval has been obtained from each of hospital administrator and co- patients to be involved in this study. Under hygienic conditions blood samples were collected anticoagulant free in order to obtain serum, which kept under -20C^{o}, then analyzed for freeT3, freeT4 and TSH as evaluation plan for thyroid function tests while these patients diagnosed with CML and set for drugs anti to the proliferation called tyrosine kinase inhibitors. Thyroid dysfunction appeared to be related to the CML itself rather than be affected with anticarcinogenic drugs, as new case subjects showed significant difference more than those of under treatment, as variation revealed.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal disorder of a pluripotent stem cell. The disease accounts for almost15% of leukemias and may occur at any age. The diagnosis of CML is rarely difficult and is assisted by the characteristic presence on the Philadelphia chromosome. It results from the t(9; 22) translocation between chromosomes 9 and 22 as a result of which part of the proto-oncogene c-ABL is moved to the BCR gene on chromosome 22 and part of chromosome 22 moves to chromosome 9. The abnormal chromosome 22 is the Ph chromosome. In the Ph translocation 5' exons of BCR are fused to the 3' exons of ABL. The resulting chimeric BCR-ABL gene codes for a fusion protein of size 210 kDa. This has tyrosine kinase activity in excess of the normal 145-kDa ABL product (Hoffbrand, 2011). Tyrosine kinase inhibitors (TKIs), the primary therapy used to manage CML, has the many treatment goals ; to induce complete clinical remissions; to prevent the progression from chronic phase to any other phase (e.g., accelerated or blast); to reduce the risk of death from disease; and to increase the quality of life of CML patients (Baccarani, 2014). TKI therapy has resulted in a 2% annual all-cause mortality rate among CML patients, a major decrease from the historical rate of 10% to 20% (Siegel, 2014), the estimated 10-year survival rate has increased from 20% to 80% (Gambacorti-Passerini, 2011). These gains in survival are only realized if CML patients remain on TKIs long-term. However, Over the course of therapy, many patients experience resistance or intolerance to TKIs, requiring a switch to a second- or third-line TKI (O'Brien, 2014). Tyrosine kinase inhibitors (TKIs) targeting the oncoprotein BCR-ABL1 have become an essential component in chronic myeloid leukemia (CML) therapy due to their success in improving patient outcomes (O'Brien, 2004; Kantarjian, 2012). There are currently several TKIs approved by the United States' Food and Drug Administration (FDA) for the treatment of patients with Philadelphia chromosome–positive (Ph +) CML in chronic phase (CML-CP) in the frontline, second-line, and later-line settings. Imatinib, nilotinib, and dasatinib are each FDA approved for the treatment of adult patients with newly diagnosed Ph+ CML-CP (Tasigna, 2015; Sprycel, 2015; Gleevec, 2015) nilotinib and dasatinib are also approved for the treatment of adults with Ph+ CML-CP with resistance to or intolerance of prior therapy including imatinib (Tasigna, 2015). Bosutinib is approved by the FDA for adult patients with Ph+ CML in any phase with resistance to or intolerance of prior therapy (Bosulif, 2013), and ponatinib is approved for the treatment of any-phase CML in adult patients with the T315I mutation or for whom no other TKI is indicated (Iclusig,

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2015). TKIs are 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 (Daub, 2010; Rios, 2011). 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 (Lodish, 2010 and Krause, 2005).

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 (Krause, 2009; Illouz, 2009; Nurmio, 2008). 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 (Krause, 2005; Illouz, 2009 and Nurmio, 2008). Little is known about the incidence of tyrosine kinase inhibitors induced thyrotoxicosis and destructive thyroiditis (Sakurai, 2010; Faris, 2007).

MATERIALS AND METHODS

A cross sectional study conducted among 1 hundred of Ph +ve CML subjects attended Khartoum oncology and nuclear medicine hospital; they were 60 female and 40 males. In this hospital treatment protocol for each established diagnosis disease is set, one of these protocols is the that for chronic myeloid leukemia, patients are regular attendants for follow up and prescription drug, ph +ve CML under glivic imitinab, for resistant glivic imitinab a restosine is set as a substitution drug for CML. Under hygienic conditions, such as extra disinfection and care patients of CML were asked for blood withdraw for analysis of thyroid function tests (FT3, FT4 and TSH). Blood samples were collected in plaincontainers without anticoagulant, allowed to clot then separation of serum with undergo analysis of TFT (FT3, FT4 and TSH), by means of a Japanese device TOHSO 360, which measures them with same principle as it a competitive enzyme immunoassay with commercial kits designed specific for that purpose, analytical phase conducted at clinical chemistry section of Khartoum oncology and nuclear hospital. Data obtained later was analyzed with statistical package of social science program-version 21.

RESULTS

The study involved onehundred (100) Ph +ve CML subjects attended Khartoum oncology and nuclear medicine hospital, they were 60 female and 40 males as in figure 1, 7% of them were new cases (they didn't start CML treatment yet), 10% were in accelerator phase (phase of transforming from chronic to acute) and the rest 83% were at the chronic phase as in Figure 2. For CML patients mean+SD for FT3 was 6.85+4.29 bringing significant difference when compared with the reference value as p value 0.0001, for FT4 mean+SD was 20.27+15.10 with obvious significant difference as value 0.0001 as well. TSH has less significant difference as p value 0.018 with mean+SD 6.86+4.76 as in Table 3-1.

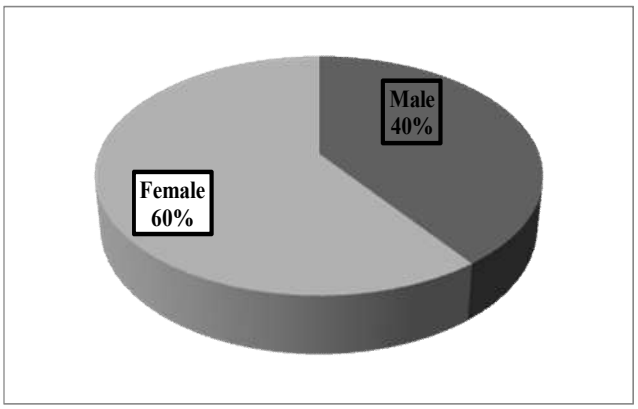

Figure 1. Male to female frequency involved in this study

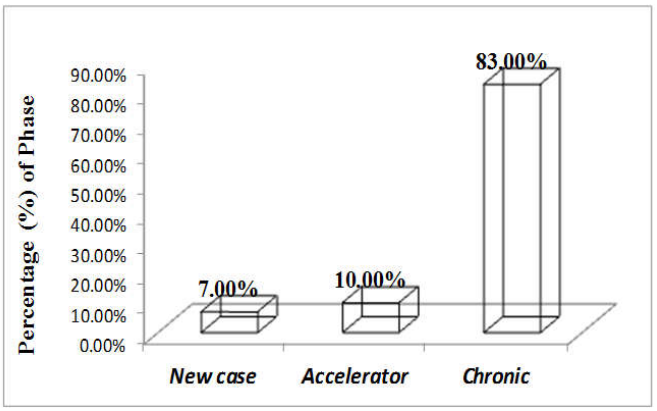

Figure 2 CML patients phases according to time of diagnosis

Table 1. TFT parameters among CML patients

Parameters	(Mean±SD) N=100	Median	R.V	*P-value*
FT3 (pg/dl)	6.8469±4.29	6.10	2.95 (2.1-3.8)	0.0001
FT4 (ng/dl)	20.27±15.10	15.94	1.21 (0.82-1.63)	0.0001
TSH (lU/ml)	6.86±4.76	1.83	2.35 (0.4-4.3)	0.018

Significant difference p value less than 0.005.

Comparison TFT among male and female in CML subjects, it didn't bring significant difference for FT3 and FT4 but an obvious significant difference obtained for TSH as in table 2.

Table 2. TFT among male and female with CML

Parameters	Male (Mean±SD)	Female (Mean±SD)	*P-value*
FT3 (pg/dl)	6.63±3.01	6.99±5.00	0.653
FT4 (ng/dl)	21.04±19.00	19.76±11.98	0.680
TSH (lU/ml)	3.68±2.23	8.99±3.53	0.010

Significant difference p value less than 0.005.

Sorting CML according to type of TKI they took, into 3categories: 83% were taking imitinab glivic, which is the regular CML treatment, 11% were new case they were not under treatment program yet and 6% were taking resitennelotinab, which was given for those with imitinab resistance as in Figure 3. Pearson correlation when conducted for CML data, several outcome were present, considering age with each TFT, it got a negative correlation with both FT4 and TSH, while positive correlation with FT3. Duration of the CML diagnosis has negative correlation with each TFT, mean while duration increases, TFT has deviation from normality. Treatment dose per day with each of TFT has negative correlation as well as in Table 4.

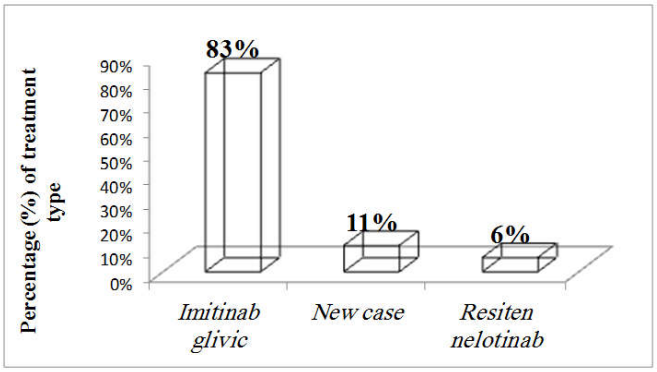

Table 3. CML patients according to TKI drug program

Table 4. Correlation of age, duration and dose of treatment with each of TFTs

Variables		FT3	FT4	TSH
Age (Years)	R-value	0.033	-0.181	-0.038
	P-value	0.748	0.072	0.709
Duration (Years)	R-value	-0.023	-0.041	-0.019
	P-value	0.819	0.687	0.851
Treat dose mg /day	R-value	-0.024	-0.029	-0.023
	P-value	0.823	0.785	0.834

Pearson correlation R (1.0 and -1)

Considering treatment program, analyzing TFT data of each group, new case, resiten nelotinab and imitinab glivic TKIs, they brought significant difference as in Table 5,6 and 7.

Table 5. CML patients under Resiten nelotinab TKI drug

Parameters	Mean±SD	R.V	*P-value*
FT3 (pg/dl)	6.60±0.83	2.95 (2.1-3.8)	0.001
FT4 (ng/dl)	18.95±7.90	1.21 (0.82-1.63)	0.000
TSH (lU/ml)	4.50±4.65	2.35 (0.4-4.3)	0.031

Significant difference p value <0.05

Table 6. CML patients under Imitinab glivic TKI drug

Parameters	Mean±SD	R.V	*P-value*
FT3 (pg/dl)	7.02±4.56	2.95 (2.1-3.8)	0.000
FT4 (ng/dl)	20.78±16.19	1.21 (0.82-1.63)	0.000
TSH (lU/ml)	6.01±17.47	2.35 (0.4-4.3)	0.001

Significant difference p value <0.05

Table 7. CML new case patients without TKIs drug

Parameters	Mean±SD	R.V	*P-value*
FT3 (pg/dl)	5.66±3.09	2.95 (2.1-3.8)	0.008
FT4 (ng/dl)	17.11±7.88	1.21 (0.82-1.63)	0.000
FSH (lU/ml)	14.58±9.02	2.35 (0.4-4.3)	0.000

Significant difference p value <0.05

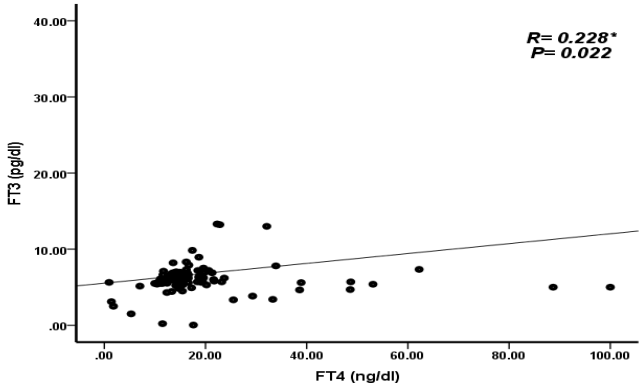

Figure 4. Correlation of FT4 and FT3

Correlation of FT3 and FT4 brought positive correlation as in figure 4, FT3 with TSH has negative correlation as in figure 5, and correlation of FT4 with TSH has positive correlation as in Figure 6.

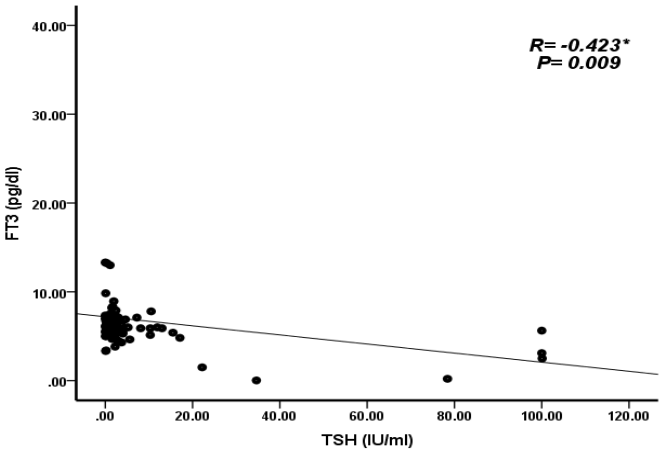

Figure 5. Correlations of FT3 and TSH

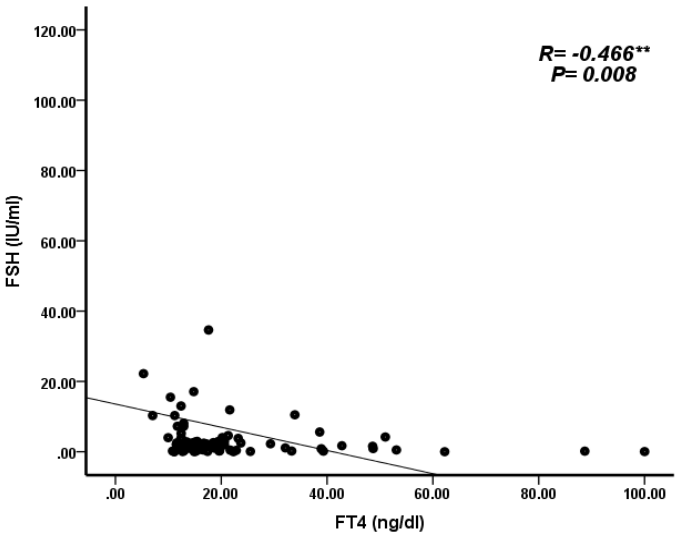

Figure 6. Correlations of FT4 and TSH

Sorting CML patients according to TFT data, 37% were with thyroid dysfunction as they sub-divided to 18% hypothyroidism, 19% hyperthyroidism and the rest with normal TFT as they were under thyroid dysfunction treatment as in Figure 7.

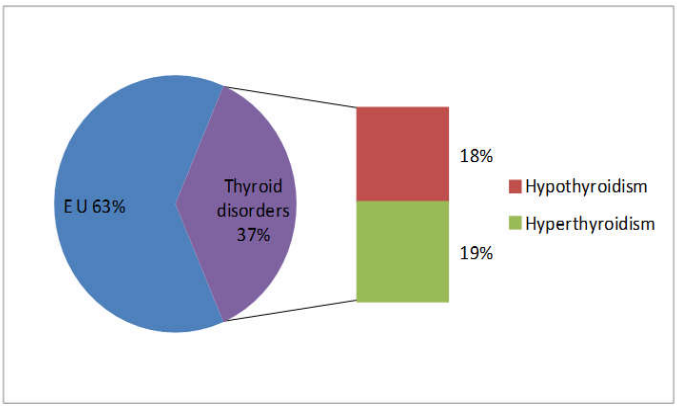

Figure 7. Sorting of CML patients according to TFT data

DISCUSSION

A main goal of CML-CP treatment with TKI therapy is to prevent disease progression to accelerated phase (AP) or blast crisis (BC) (21). In cases of early treatment failure, it recommend considering a switch in therapy as well as other evaluations (eg, assessing treatment adherence, testing for the presence of BCR-ABL1 mutations associated with TKI resistance). One reason for considering a switch in therapy is resistance to frontline therapy. Primary resistance (a lack of an initial response to treatment) is indicated by missing key early response landmarks (NCCN, 2016; Baccarani, 2006). Primary resistance to TKI therapy is not fully understood and has been hypothesized to result from a variety of factors (eg, those affecting intracellular TKI concentrations and bioavailability (Gambacorti-Passerini, 2014; White, 2010; Mahon, 2008 and Hegedus, 2009), activation of compensatory signaling (Bixby, 2011).

Secondary resistance is defined as the loss of a previously established treatment response. Patients with treatment-resistant disease are at an increased risk of events such as loss of response and are less likely to achieve longer-term molecular response goals (Branford, 2012 and Quintas-Cardama, 2009). In addition to reduced long-term outcomes, patients who fail to reach NCCN or ELN response milestones have a greater risk of progression to advanced disease and reduced survival (Quintas-Cardama, 2009; Marin, 2008; Alvarado, 2009). In this study, considering some kind effects of TKIs may occurred, TFTs were tested, FT3, FT4 and TSH among patients who involved in this study, it revealed thyroid dysfunction among 37% of CML subjects, 18% were hypothyroidism and 19 were hyperthyroidism, 83% of the CML patients under imitinab TKI drug, 7 were under Resiten nelotinab, while 10% were TKIs free protocol, transferring from imitinab to nelotinab due to resistance to main TKI drug, which is imitinab.

TFT assessed among CML patients revealed no significant difference for both FT3 and FT4, while asignificant difference obtained for TSH. Considering TKIs and taking drugs, new cases, imitinab glivic and resiten nelotinab, each of FT3, FT4 and TSH brought significant difference, the same finding from a study conducted at the same manner; it showed that some significant changes on thyroid function tests during imatinib therapy (Mohammad, 2014). And disagreement obtained with finding of a study also measured the same hormones and didn't find any changes in TFT during treatment with imitinab (AbolghasemAllahyari, 2016). Our findings may direct the concept of thyroid dysfunction may occur non- relative to drug induced, and that matches the suggestion of a study said that TKI can induce thyroid dysfunction (HalaAhmadieh, 2012).

Some of patients in this study were presented hypothyroidism and same frequency for hyperthyroidism, this agrees with a review studyobservation, it revealed that TKIs through blocking molecular pathways, could induce thyroid abnormalities including hypothyroidism and less often hyperthyroidism (Georgios Boutzios, 2017). As our findings show changes in TFT with second generation TKI, nelotinab, it agrees with other study conducted on ph+ve CML subjects (Thieo Daneil Kim, 2010).

Conclusion

Thyroid dysfunction is a reality among chronic myeloid leukemia, whether they were on treatment program or not as new cases.

Recommendations

Thyroid dysfunction therapy should be administrated with continual follow up of TFTs.

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