

Impact of Hydroxyurea Treatment on Thyroid Function Profile Among Chronic Myeloid Leukemia Patients in Khartoum Nuclear and Radiology Hospital

AYMAN ALI MOHAMMED ALAMEEN^{1,2*}, SAMWAL ALOBID MOHAMMED², YASAMIN AL-QASSAB³, ABUALGASIM ELGAILI ABDALLA^{1,4}, KHALID OMER ABDALLA ABOSALIF^{1,4}

¹Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Sakaka, Saudi Arabia.

²Department of Clinical Chemistry, Faculty of Medical Laboratory Science, University of Khartoum, Khartoum, Sudan.

³Department of Anatomy, College of Medicine, University of Baghdad, Baghdad, Iraq.

⁴Department of Medical Microbiology, Faculty of Medical Laboratory Sciences, Omdurman Islamic University, Omdurman, Sudan

*Correspondence: Dr. Ayman Ali Mohammed Alameen, E-mail: aymoon28@gmail.com; Tel: +966 53 2276447

ABSTRACT

Aim: To assess thyroid function hormones among chronic myeloid leukemia patients under hydroxyurea treatment

Method: This cross-sectional study was conducted on CML patients using hydroxyl urea treatment protocol during a period from March to August 2019 at Khartoum nuclear and radiology hospital. Total 100 participants, 53% females and 47% males between 11 to 70 years of age were assessed for thyroid function parameters including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4).

Results: This study revealed that the thyroid hormones levels were increased among CML patients when compared with reference values. In addition, there was strong correlation between duration of drug usage and thyroid hormones levels. However, there was no statistical significant difference between hormones levels and gender.

Conclusion: This study concluded that hydroxyurea treatment can increase thyroid hormones levels which may cause a serious metabolic disorders among CML patients.

Keywords: Chronic myeloid leukemia; Thyroid hormones; Hydroxyurea

INTRODUCTION

The thyroid gland is the biggest endocrine gland in the human body producing two hormones which have a crucial role in various aspects of metabolism¹ and regulate cellular growth and development^{2,3,4}. Triiodothyronine (T3), is a powerful regulator of a variety of physiological activities, including cellular metabolic rate, heart, and digestive functions, muscle function, brain development, and bone maintenance^{5,6}. Nevertheless, defect in regulation of these hormones secretion or function could lead to many disorders such as cardiovascular disease^{7,8}, diabetes mellitus^{9,10} and chronic liver disease^{11,12}.

Chronic myeloid leukemia (CML), is a myelogenous disorder characterized by a massive production of immature proliferative white blood cells due to a genetic mutation in the hematopoietic stem cell^{13,14,15}. CML comprises 30% of all types of leukemia, 20% of cases occur among patients younger than 25 years and 10% being in patients with age less than 20 year old. The frequent of CML is slightly predominant in males than females (1.4/1.3)^{16,17}. CML is most commonly treated with electromagnetic waves (X-ray) or conventional chemotherapeutic drugs such as Busulfan and Hydroxyurea. Hydroxyurea drug containment the proliferation of myeloid tissue resulting in significant good prognosis during the chronic phase of the disease, with a limited effect on overall survival^{18,19}. Therefore, the main objectives from CML treatment protocols were the extension of survival and increase the probability of being ready to stem cell transplantation, then cure^{20,21,22}.

Tyrosine kinase inhibitors has well documented deteriorious effect in thyroid function²³. Hydroxyurea has tyrosine kinase inhibitor activity²⁴, therefore, it may have an impact on thyroid function.

METHODS

This descriptive cross-sectional study was conducted during a period from March to August 2019 at Khartoum nuclear and radiology hospital. One hundred blood samples were obtained from Sudanese patients with chronic myeloid leukemia under hydroxyurea treatment protocol. Plasma was obtained and stored at -20°C until processing. Thyroid hormones including FT3, FT4 and TSH concentrations were measured via competitive immunoassay. Tests were performed according to manufacturer's direction (TOSOH, Japan). Data obtained was analyzed with SPSS program version 20. T-test and cross-tab were used to determining the significant difference and correlation, respectively.

RESULTS

This descriptive cross-sectional study was conducted to determine the impact of Hydroxyurea on the level of thyroid hormones. One hundred blood samples were taken from CML patients under Hydroxyurea treatment regimen, 53% were females and 47% were males. Patient's age range from 11 years to 77 years (mean±SD 38.19±14.26), 44% were more than 40 years old and 56% were less than 40 years (Table-I). Duration of initial exposed to Hydroxyurea treatment between 1 and 4 years (mean±SD 1.48±1.05).

This study showed that the levels of thyroid hormones including FT3, FT4 and TSH were markedly increased in CML patients under treatment of chemotherapy when

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compared with reference values ($P < 0.01$) (Table-II). High levels of hormones were positively correlate with duration of treatment (Table-III)

This study demonstrated that there was no any effects of gender and age groups on the levels of hormones among Hydroxyurea CML treated patients (Table-IVa and IVb).

Table-I: Frequency distribution of patients according to age/gender

Age (Years)		Gender	
Less than 40	More than 40	Male	Female
56 %	44%	47%	53%

Table-II: Mean comparison of study parameters with reference values

Parameters	Case (Mean±SD)	Mean (R.V)	P-value
FT3	4.74±1.18	2.95 (2.1-3.8 ng/dl)	0.000
FT4	18.09±5.64	1.23 (0.82-1.63 ng/dl)	0.000
TSH	2.88±1.76	2.35 (0.4-4.3 IU/ml)	0.003

Table-III: Correlation between duration of drug-using and TFT parameters

Duration of hydroxyurea treatment(Years)	FT3	FT4	TSH
1 – 2	0.210	0.163	0.124
2 – 4	0.834	0.105	0.218

Table-IVa: Mean comparison of study parameters within genders

Parameters	Male (Mean±SD)	Female (Mean±SD)	P-value
FT3	4.52±1.25	4.94±1.09	0.081
FT4	18.35±5.06	17.86±6.14	0.662
TSH	3.13±1.88	2.66±1.64	0.186

Table-IVb: Mean comparison of study parameters within age groups

Parameters	<40 Years (Mean±SD)	>40 Years (Mean±SD)	P-value
FT3	4.84±1.08	4.61±1.29	0.332
FT4	18.73±5.88	17.27±5.26	0.194
TSH	2.92±1.83	2.83±1.69	0.808

DISCUSSION

CML, distributed worldwide with incidence rate 1–2 cases per 100 000 population, which rate of frequency is fairly constant in various countries. The disease can affect any age, but slightly increased at age group 50-60 years old with predominant among males¹⁷. Hydroxyurea (Hydrea; hydroxycarbamide) is one of the most effective antimetabolite drugs for treatment of CML upto date. However, it has detrimental effects on tyrosine kinase signaling pathways which may lead to dysregulation of hormone systems²⁵. The impact of long term using of hydroxyurea treatment alone in CML patients on thyroid function need to be determined.

Tyrosine-kinase inhibitors drugs are initially causing hyperthyroidism followed by hypothyroidism²⁶. The present study found that treatment of CML patients with hydroxyurea for 1 year or more can dramatically increased the thyroid hormones such as FT3, FT4 and TSH. This findings was disagree with study reported that hydroxyurea causes decrease of TSH and T4²⁷. Previously, it was documented that hydroxyurea can mediate thyroid

dysfunction including both hypothyroidism (10%) and hyperthyroidism in 3% of treated patients²⁸. The variation of the results displayed by different investigators could be due to differences in clinical cases, severity of the disease and duration of exposed to treatment. Taken all, hydroxyurea treatment clearly causes thyroid dysfunction.

CONCLUSION

This study conclude that use of hydroxyurea for treatment of CML patients results in elevation of thyroid hormones concentration.

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