DOI: https://doi.org/10.31351/vol34iss2pp40-46

Serum Levels of Advanced Oxidation Protein Products and some Liver Function Markers in Chronic Myeloid Leukemia-Chronic Phase Patients Receiving Imatinib or Nilotinib

Ekhlas Khammas Hasan[1*], Ali Abdulhussain Kasim[2] and Bassam Francis[3]

[1] Department of Clinical Pharmacy, College of Pharmacy, Al-Bayan University, Baghdad, Iraq.
[2] Department of Clinical Laboratory Sciences, College of Pharmacy, University of Baghdad, Baghdad-Iraq.
[3] Ministry of Health, Hematology and Bone Transplant Center, Medical City, Baghdad, Iraq.

[*]**Corresponding author**
Received 27/8/2023, Accepted 28/1/2025, Published 25/6/2025

Abstract

The treatment of chronic myeloid leukemia has witnessed substantial advancements by the introduction of tyrosine kinase inhibitors. Oxidative stress has been proposed as potential mechanism for resistance to the action of tyrosine kinase inhibitors. Simultaneously, oxidative stress has a crucial role in hepatic diseases and medication-induced hepatotoxicity. The study aims to investigate the serum levels and potential correlation of the advanced oxidation protein products (AOPPs), as indicator of oxidative stress, with some markers of liver function, in patients receiving TKIs, namely imatinib or nilotinib. A total of 76 chronic myeloid leukemia-chronic phase patients were enrolled in this cross-sectional, single center study. The enrolled patients were grouped as those receiving imatinib, at an oral dose of 400 mg/ day, and those who failed to clinically respond to imatinib and were switched to nilotinib, at an oral dose of 800 mg/ day. Serum levels of the advanced oxidation products (AOPPs), the hepatic enzymes alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total serum bilirubin (TSB) as well as direct and indirect bilirubin were measured. The enrolled patients in both groups were of comparable age and gender; P>0.05. Serum ALT level was significantly higher in patients receiving imatinib compared to those receiving nilotinib; by contrast, serum AOPPs, total and direct bilirubin levels were significantly lower in patients receiving imatinib compared to those receiving nilotinib. There was no significant correlation between the serum levels of AOPPs and that of liver function markers whether in the pooled data of total participants or based on the type of medication used. In conclusion, the oxidative stress, indicated by AOPPs, and bilirubin metabolism is significantly deranged in chronic myeloid leukemia-chronic phase patients receiving nilotinib as compared to those receiving imatinib.

Keywords: Chronic myeloid leukemia, Hepatotoxicity, Imatinib, Nimotinib, Oxidative stress.

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder. The condition is primarily caused by a genetic anomaly known as the Philadelphia chromosome, resulting from a definite genetic translocation between chromosomes 9 and 22. The rearrangement gives rise to a fusion gene called BCR-ABL1, which produces a protein with abnormal tyrosine kinase activity called BCR-ABL1 kinase that disrupts the normal development and programmed cell death of myeloid cells, leading to uncontrolled proliferation of these primitive hemopoietic stem cell.[1] The presence of BCR - ABL1 gene has been found to affect several genes in CML patients.[2, 3] CML typically progresses slowly and can be divided into three phases: chronic (CP), accelerated (AP), and blast phases (BP). In the CML-CP, patients may not exhibit significant symptoms, and the condition is often detected incidentally through routine blood tests. As CML advances to the accelerated and blast phases, the number of immature white blood cells increases, resulting in more pronounced symptoms such as fatigue, weight loss, abdominal discomfort, splenomegaly, and bone pain. [4]

The treatment of CML has witnessed substantial advancements in recent times. Targeted therapy using tyrosine kinase inhibitors (TKIs),

including imatinib, nilotinib, dasatinib, bosutinib and ponatinib, has transformed the management of CML. These medications specifically target and inhibit the abnormal BCR-ABL1 kinase, reducing the number of cancer cells and enabling patients to achieve long-term remission. However, long-term use of TKI is accompanied by persistent drug adverse events such as increased risk of bleeding, anemia, hematological toxicity, edema, fluid retention, hepatic toxicity, increased serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), gastrointestinal disorders, bone pain, muscle cramps/spasms, and musculoskeletal pain; that affect the quality of life of patients, thereby affecting patient compliance and treatment efficacy.[5-7] In some cases, allogeneic stem cell transplantation may be considered, particularly for individuals who do not respond well to TKIs or cannot tolerate them.[8] Oxidative stress has been proposed as potential mechanism for TKIs resistance.[9, 10]

TKIs therapy has been associated with hepatotoxicity ranging from transient and usually asymptomatic elevations in serum enzymes and abnormal liver function tests, to acute liver failure; along with chronic hepatitis B reactivation. Liver enzymes need to monitor in CML patients receiving TKIs. [11]

Simultaneously, oxidative stress has a crucial role in hepatic diseases and medication-induced hepatotoxicity. [12-14]The study aims to investigate the serum levels and potential correlation of the advanced oxidation protein products (AOPPs), as indicator of oxidative stress, with some markers of liver function to assess the differences in serum levels of these markers between patients receiving imatinib and those receiving nilotinib.

Patients and Methods

This cross sectional, single center study was carried out in the National Center of Hematology, Baghdad Teaching Hospital, Medical City, Baghdad; Iraq. This center serves a diverse range of patients from several governorates total of 76 CML-CP patients that were already diagnosed by hematologists (according to the European LeukemiaNet (ELN) recommendations) [١٤] were enrolled in the study. The study was continued for nine months from May 2022 to the end of January 2023.

The study was approved by the Ethics Committee of the College of Pharmacy, University of Baghdad; with the number (RECACPUB-3102020B). All participants were informed about the purpose and the expected benefits of the study; a written consent of participation was documented.

The enrolled individuals were adult confirmed CML-CP patients, receiving either imatinib, at an oral dose of 400 mg/ day, or those who failed to clinically respond to imatinib (i.e., imatinib-resistant) and were switched to nilotinib, at an oral dose of 800 mg/ day; according to ELN recommendations [15]. Patients were on those medications for at least 12 months; and all patients are clinically responsive to their current medication according to a recent monitoring of molecular response by BCR-ABL1 measurement.

The exclusion criteria were receiving interferon-alpha or hydroxyurea, history hematopoietic stem-cell transplantation, uncontrolled cardiovascular diseases or diabetes mellitus, chronic infections, other type of cancer, pregnancy, supplementation with vitamins with antioxidant potentials, and congenital bleeding disorders or acquired bleeding disorders that were reported prior the administration of imatinib or nilotinib.

A blood sample (5ml) was collected from each participant and serum was separated and used for the measurement of AOPPs, the hepatic enzymes alkaline phosphatase (ALP), ALT, and AST, and total serum bilirubin (TSB) as well as direct and indirect bilirubin. Serum AOPPs level was measured by enzyme-linked immunosorbent assay (ELISA) using human AOPP ELISA kit purchased from (BT-LAB /China). Serum levels of liver enzymes and bilirubin were measured by enzymatic colorimetric method using the corresponding kits purchased from (Beacon Diagnostic /India).

Statistical analysis

Data analysis was performed using SPSS software for Windows version 26.0. Shapiro-Wilk test was employed to determine whether data were normally distributed. The data were normally distributed, and parametric statistics were employed. Categorical variables were presented as number and percentage; while, continuous variables were presented as mean ± standard deviation (SD). Unpaired t-test was used to evaluate the difference between the mean of two groups; chi-square was used to study the association of categorical variables. Pearson's correlation test was used to study the correlation of variables. A P-value <0.05 was considered statistically significant.

Results and Discussion

Chronic myeloid leukemia-CP patients that were eligible and completed the study requirements were 39 female and 37 male, with an age range (21-75years); as shown in figure1.

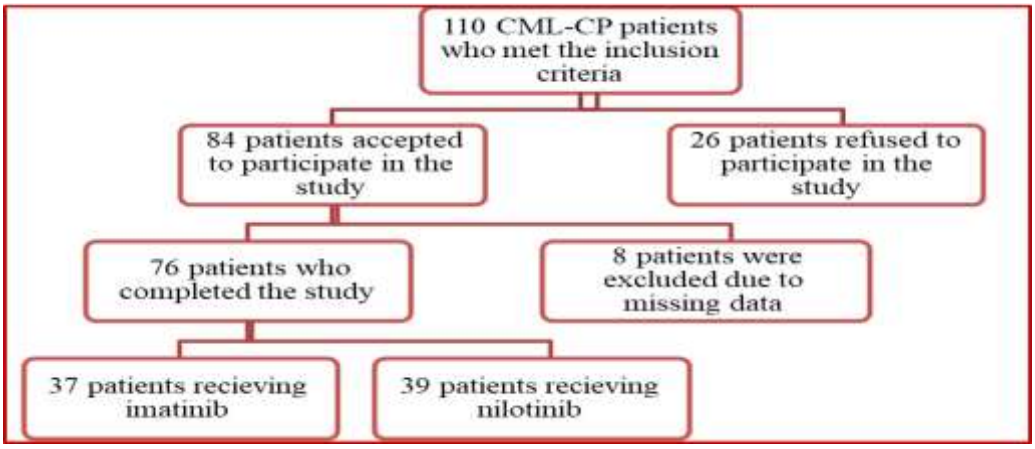

Figure1. Schematic representation of the paticipants' selection.

There was no statistical significant difference between patients receiving imatinib or nilotinib with regard to age or gender, (P> 0.05); as shown in Table 1.

Table 1. Demographic characteristics of the participants

Variable		Patients receiving imatinib (n=37)	Patients receiving nilotinib (n=39)	P-value
Age (years)		44.19±13.05	47.10±10.31	0.074
Gender	**Male n(%)**	17 (45.95)	20 (51.28)	0.6
	Female n(%)	20 (54.05)	19 (48.72)	

Where: *n, number*

Serum levels of AOPPs, ALT, TSB, and direct bilirubin were significantly different between patients receiving imatinib and those receiving nilotinib; where serum ALT level was higher, and serum AOPPs, total and direct bilirubin levels were lower in patients receiving imatinib compared to those receiving nilotinib; as shown in Table 2.

Table 2. Serum levels of the advanced oxidation protein products and the studied liver function markers of participants

Variable	Patients receiving imatinib (n=37)	Patients receiving nilotinib (n=39)	P-value
AOPPs (ng/ml)	6.64± 2.28	8.57±0.55	**0.007***
ALP (IU/L)	161.89 ±42.89	153.46 ±42.97	0.3
ALT (IU/L)	13.89 ±3.54	11.87±2.70	**0.006***
AST (IU/L)	11.54±3.63	11.62±2.33	0.9
TSB (mg/dl)	0.92±0.319	1.10±0.42	**0.04***
Indirect bilirubin (mg/dl)	0.511±0.22	0.55±0.27	0.4
Direct bilirubin (mg/dl)	0.41±0.16	0.56±0.27	**0.005***

Where: n, number; AOPPs, advanced oxidation protein products; ALP, alkalin phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TSB, total serum bilirubin. * statistically significant (P< 0.05)

There was no significant correlation between the serum levels of AOPPs and that of liver function markers whether in the pooled data of total participants (Table 3) or based on the type of TKIs used (Table 4); P-value >0.05.

Table 3. Correlation of the advanced oidation protein products with the studied liver function markers of total participants

Variables	r-value	P-value
ALP	-0.166	0.151
ALT	-0.055	0.635
AST	0.160	0.167
TSB	-0.013	0.914
Direct bilirubin	-0.084	0.472
Indirect bilirubin	0.064	0.585

Where: ALP, alkalin phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TSB, total serum bilirubin. r, Pearson's correlation coefficient.

Table 4. Correlation of the advanced oxidation protein products with the studied liver function markers of

participants per type of medication

Variables	Patients receiving imatinib (n=37)		Patients receiving nilotinib (n=39)	
	r-value	P-value	r-value	P-value
ALP	-0.281	0.092	-0.066	0.688
ALT	0.097	0.558	0.003	0.984
AST	0.078	0.648	0.266	0.102
TSB	0.039	0.818	-0.160	0.330
Direct bilirubin	-0.028	0.868	-0.281	0.083
Indirect bilirubin	0.063	0.709	0.046	0.781

Where: ALP, alkalin phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TSB, total serum bilirubin. r, Pearson's correlation coefficient.

The success rates in the management of CML have been improved since the discovery of TKIs. Nevertheless, these medications are not free of adverse events that can impact the quality of life of patients.[5-7,16]

Generally, women are more prone to the development of adverse drug reactions than men; this predisposition is not well understood, however the gender-specific difference in medications pharmacokinetics has been proposed.[17, 18] In the present study, the effect of age and gender is eliminated as participants were of comparable age and of male and female distribution in the two study groups.

Chronic oxidation is a key player in cancer initiation and development.[19] Gào *et al.* in a systematic review of literature reviews described about 20 pathways by which oxidative stress participates in cancer initiation and development by mediating molecular damage as well as disruption of reduction-oxidation (redox) signaling. Those pathways are related to reactive oxygen and nitrogen species generating organelles and enzymes, kinases/phosphatases signal transduction cascades and transcription factors. [20]

Oxidative stress has been reported to have a crucial role in the pathogenesis and progression of CML mediated by a wide range of effects. To begin with, oxidative stress participates in DNA damage, instability, and genetic mutation. Moreover, it modulates cell signaling thus disturbing cellular growth, survival, and apoptosis. Additionally, oxidative stress mediates resistance to medications, inflammation within bone marrow microenvironment, and transformation of CML-CP to the more aggressive CML-BP.[11, 21-23]

Several markers are utilized as indicators of oxidative stress [24]; among these indicators are the AOPPs that possess proinflammatory potentials.[25]Ammar *et al.* has reported that serum AOPPs levels are higher in imatinib-resistant CML patients compared to the non-resistant patients.[11] This occurs in accordance with findings of the present study; where serum levels of AOPPs were significantly lower in the imatinib-treated patients than that in the nilotinib-treated patients. In the present study, the patients in the nilotinib-treated group were switched to this medication for being imatinib-resistant.

Hepatotoxicity is a common adverse effect in TKIs-treated patients, with relative differences in this regard among individual agents. [26] The exact mechanism behind TKI-related liver damage remains uncertain. It has been proposed that the development of reactive metabolites during their metabolism is a critical factor in the hepatotoxicity induced by TKIs. These metabolites can irreversibly bind with important cellular components, such as proteins, lipids, and DNA leading to irriversible cellular damage.[27] Immune-mediated reactions has been also proposed to mediate TKIs-induced hepatotoxicity.[28] Moreover, some TKIs were reported to interfere with the conjugation of the endogenous toxic metabolite, bilirubin, by inhibiting UDP-glucuronosyltransferase, specifically the isoform UGT1A1 and thus can result in accumulation of bilirubin with subsequent hyperbilirubinemia and jaundice.[29, 30] By an *in-vitro* study, Ai L *et al.* showed that nilotinib is a potent inhibitor of UGT1A1.[31] However, *UGT1A1* gene has been reported to have number of polymorphisms that can results in variability in response to the inhibitory effect of nilotinib on UGT1A1.[32]

In the present study, serum levels of ALT, TSB, and direct bilirubin were significantly different between patients receiving imatinib and those receiving nilotinib; where serum ALT level was higher, and total and direct bilirubin levels were lower in patients receiving imatinib compared to those receiving nilotinib. This indicates that the effect of TKIs on liver function of CML patients is dependent on the individual agent used for treatment. In a systematic review and meta-analysis, Wang *et al.* has reported that CML patients receiving the newer TKIs are at higher risk of

hepatotoxicity than those using imatinib; furthermore, the TKIs-induced hepatotoxicity is dose dependent. [26] In the present study, serum AOPPs levels showed no significant correlation with the studied markers of liver function. Despite oxidative stress has been shown to have a crucial role in hepatic diseases[12] , it does not seems to participate in alterations of the liver function markers in CML patients receiving imatinib or nilotinib.

Conclusion

The oxidative stress, indicated by AOPPs, and bilirubin metabolism is significantly deranged in CML-CP patients receiving nilotinib as compared to those receiving imatinib.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics Statement

The study was approved by the Ethics Committee of the College of Pharmacy, University of Baghdad; with the number (RECACPUB-3102020B).

References

1. Abdulmawjood B, Costa B, Roma-Rodrigues C. Genetic Biomarkers in Chronic Myeloid Leukemia: What Have We Learned So Far? International journal of molecular sciences. 2021;22(22):12516.
2. Khaleel AW, Altaee MF. Ltb4r Gene Expression in Chronic Myeloid Leukemia in Iraq. Iraqi Journal of Science. 2023;64(5):2202-14.
3. Aljoubory HM, Altaee MF. Correlation study between three different genes expression and chronic myeloid leukemia in Iraq. Iraqi journal of agricultural sciences. 2021;52(3):611-9.
4. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. 2020;95(6):691-709.
5. Chow EJ, Doody DR, Wilkes JJ, Becker LK, Chennupati S. Adverse events among chronic myelogenous leukemia patients treated with tyrosine kinase inhibitors: a real-world analysis of health plan enrollees. 2021;62(5):1203-10.
6. Inzoli E, Aroldi A, Piazza R, Gambacorti-Passerini C. Tyrosine Kinase Inhibitor discontinuation in Chronic Myeloid Leukemia: eligibility criteria and predictors of success. 2022;97(8):1075-85.
7. Abdul-Razq MH , Al-Amili WA, Abdul Hussein Moyet, Al-Faisal AM, Abdulhassan IA, Jumaah SS. Influence of multi-drug transporter gene ABCG2 polymorphism (C421A) in clinical out care in some Iraqi chronic myeloid leukemia patients treated with imatinib mesylate. Iraqi Journal of Biotechnolog. 2017;16(3):98-107.
8. Niederwieser C, Kröger N. Transplantation in CML in the TKI era: who, when, and how? Hematology American Society of Hematology Education Program. 2022;2022(1):114-22.
9. Głowacki S, Synowiec E, Szwed M, Toma M, Skorski T, Śliwiński T. Relationship between Oxidative Stress and Imatinib Resistance in Model Chronic Myeloid Leukemia Cells. Biomolecules. 2021;11(4):610.
10. 10.Ammar M, Ben Mahmoud L. Relationship of oxidative stress in the resistance to imatinib in Tunisian patients with chronic myeloid leukemia: A retrospective study. Journal of clinical laboratory analysis. 2020;34(2):e23050.
11. Hadi AM, AL-Malki FH, Ali SH. The Effect of Selectivity of Inhibitors to Cox-2 Enzyme on Hepatobiliary and Platelet Function in Patients with Osteoarthritis. Journal of the Faculty of Medicine Baghdad. 2009;51(4):437-41.
12. Cichoż-Lach H, Michalak A. Oxidative stress as a crucial factor in liver diseases. World journal of gastroenterology. 2014;20(25):8082-91.
13. Abd Al-Zahra JI, Ismael DK, Al-Shawi NN. Preventive Effects of Different Doses of Pentoxyfilline Against CCl4-Induced Liver Toxicity in Rats. Iraqi journal of pharmaceutical sciences.2009; 18(Suppl.):39-46.
14. Attyah AM, Ismail SH. Protective Effect of Ginger Extract Against Cisplatin-Induced Hepatotoxicity and Cardiotoxicity in Rats. Iraqi journal of pharmaceutical sciences. 2012; 21(1):27-33.
15. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.
16. Hassan EF, Kadhim DJ, Younus MM. Safety profile of biological drugs in clinical practice: a retrospective pharmacovigilance study. Iraqi journal of pharmaceutical sciences. 2022;31(1):32-42.
17. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biology of sex differences. 2020;11(1):32.
18. Alsaedi AA, Younus MM, Kadhim DJ. Gender Differences in Adverse Drug Reactions Among Adult Patients Reported to the Iraqi Pharmacovigilance Center. Iraqi journal of pharmaceutical sciences. 2021;30(2):249-60.
19. Ali ZM, Ali SH, Mohsen FY. Assessment of Some Hematological parameters in Iraqi Women with Different Breast Cancer Stages. Iraqi Journal of Pharmaceutical Sciences. 2020;29(2):99-106.
20. Gào X, Schöttker B. Reduction-oxidation pathways involved in cancer development: a

systematic review of literature reviews. Oncotarget. 2017;8(31):51888-51906.
21. Pascu VÎnturiȘ EG, GĂman AM. Assessment of Oxidative Stress in Patients with Chronic Myeloid Leukemia Depending on Associated Comorbidities. Current health sciences journal. 2020;46(1):23-30.
22. Dikić D, Bogdanović A, Marković D. Inflammation Promotes Oxidative and Nitrosative Stress in Chronic Myelogenous Leukemia. 2022;12(2):247.
23. Pande D, Negi R, Karki K, Khanna RS, Khanna HD. Oxidative damage and cell signaling transduction in patients of chronic myeloid leukemia. Acta biochimica et biophysica Sinica. 2015;47(6):474-6.
24. Peluso I, Palmery M, Pérez-Jiménez J, Drummen G. Biomarkers of Oxidative Stress in Experimental Models and Human Studies with Nutraceuticals: Measurement, Interpretation, and Significance. Oxidative medicine and cellular longevity. 2016;2016:6159810.
25. Piwowar A. [Advanced oxidation protein products. Part I. Mechanism of the formation, characteristics and property]. Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego. 2010;28(164):166-9.
26. Wang Z, Wang X, Wang Z, Feng Y, Jia Y, Jiang L, et al. Comparison of Hepatotoxicity Associated With New BCR-ABL Tyrosine Kinase Inhibitors vs Imatinib Among Patients With Chronic Myeloid Leukemia: A Systematic Review and Meta-analysis. JAMA network open. 2021;4(7):e2120165.
27. Teo YL, Ho HK, Chan A. Formation of reactive metabolites and management of tyrosine kinase inhibitor-induced hepatotoxicity: a literature review. Expert opinion on drug metabolism & toxicology. 2015;11(2):231-42.
28. Kijima T, Shimizu T, Nonen S, Furukawa M, Otani Y, Minami T, et al. Safe and successful treatment with erlotinib after gefitinib-induced hepatotoxicity: difference in metabolism as a possible mechanism. Journal of clinical oncology: Official journal of the American Society of Clinical Oncology. 2011;29(19):e588-90.
29. Zhang D, Chando TJ, Everett DW, Patten CJ, Dehal SS, Humphreys WG. In vitro inhibition of UDP glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. Drug metabolism and disposition: the biological fate of chemicals. 2005;33(11):1729-39.
30. Liu Y, Ramírez J, House L, Ratain MJ. Comparison of the drug-drug interactions potential of erlotinib and gefitinib via inhibition of UDP-glucuronosyltransferases. Drug metabolism and disposition: the biological fate of chemicals. 2010;38(1):32-9.
31. Ai L, Zhu L, Yang L, Ge G, Cao Y, Liu Y, et al. Selectivity for inhibition of nilotinib on the catalytic activity of human UDP-glucuronosyltransferases. Xenobiotica; the fate of foreign compounds in biological systems. 2014;44(4):320-5.
32. Court MH, Freytsis M, Wang X, Peter I, Guillemette C, Hazarika S, et al. The UDP-glucuronosyltransferase (UGT) 1A polymorphism c.2042C>G (rs8330) is associated with increased human liver acetaminophen glucuronidation, increased UGT1A exon 5a/5b splice variant mRNA ratio, and decreased risk of unintentional acetaminophen-induced acute liver failure. The Journal of pharmacology and experimental therapeutics. 2013;345(2):297-307.

مستويات نواتج اكسدة البروتين المتقدمة وبعض علامات وظائف الكبد في المصل لدى مرضى سرطان الدم النخاعي المزمن - المرحلة المزمنة الذين يتلقون إيماتينيب أو نيلوتينيب

إخلاص خماس حسن *[1]، علي عبد الحسين قاسم[2] وبسام فرنسيس[3]

[1] فرع الصيدلة السريرية، كلية الصيدلة، جامعة البيان، بغداد، العراق
[2] فرع العلوم المختبرية السريرية، كلية الصيدلة، جامعة بغداد، بغداد،العراق
[3] وزارة الصحة ،مركز أمراض الدم وزراعة العظام، مدينة الطب، بغداد، العراق

الخلاصة:

شهد علاج سرطان الدم النخاعي المزمن تطورات كبيرة منذ البدء باستخدام مثبطات التيروزين كينيز. تم اقتراح الإجهاد التأكسدي كآلية محتملة لمقاومة تأثير مثبطات التيروزين كينيز. وفي نفس الوقت فان للإجهاد التأكسدي دور حاسم في أمراض الكبد وفي تلف خلايا الكبد.
تهدف الدراسة إلى التحقق من مستويات نواتج اكسدة البروتين المتقدمة في المصل، كمؤشر على الإجهاد التأكسدي، وارتباطها المحتمل مع بعض علامات وظائف الكبد في المرضى المعالجين بنوعين من مثبطات التيروزين كينيز وهما الايماتينيب والنيلوتينيب . تم تسجيل مجموع ٧٦ من مرضى سرطان الدم النخاعي المزمن - المرحلة المزمنة في هذه الدراسة المستعرضة والجارية في مركز واحد. تم تصنيف المرضى المشاركين في الدراسة الى مجموعتين؛ مجموعة يتلقون عقار الايماتينيب، بجرعة فموية ٤٠٠ مجم يوميا ، ومجموعة الذين فشلوا في الاستجابة سريريًا للإيماتينيب وتم تحويلهم إلى عقار النيلوتينيب بجرعة فموية قدرها ٨٠٠ مجم يوميا. تم قياس مستويات نواتج اكسدة البروتين المتقدمة والإنزيمات الكبدية الفوسفاتيز القلوي (ALP) والألانين أمينوترانسفيراز (ALT) والأسبارتات أمينوترانسفيراز (AST) وإجمالي البيليروبين في المصل (TSB) وكذلك البيليروبين المباشر وغير المباشر في المصل. كان المرضى في كلا المجموعتين متقاربين من ناحية العمر والجنس$P>0.05$. كان مستوى ALTفي المصل أعلى في المرضى الذين يتلقون الايماتينيب مقارنة هؤلاء المتلقين للايماتينيب؛ بينما كانت مستويات نواتج اكسدة البروتين المتقدمة

ومستويات البيليروبين الكلي والمباشر أقل في المرضى الذين يتلقون الايماتينيب مقارنة مع هؤلاء الذين يتلقون النيلوتينيب. لم يكن هناك ارتباط معنوي بين مستويات نواتج اكسدة البروتين المتقدمة وعلامات وظائف الكبد سواء في البيانات المجمعة من إجمالي المشاركين أو بناءً على نوع العقار المستخدم. كاستنتاج فإن الإجهاد التأكسدي ، المشار إليه بمستويات نواتج اكسدة البروتين المتقدمة، واستقلاب البيليروبين مختل بشكل اكبر في مرضى سرطان الدم النخاعي المزمن - المرحلة المزمنة الذين يتلقون عقار النيلوتينيب مقارنة مع هؤلاء الذين يتلقون عقار النيلوتينيب.

الكلمات المفتاحية: سرطان الدم النخاعي المزمن، السمية الكبدية، إيماتينيب، نيلوتينيب، الإجهاد التأكسدي.