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A theoretical and practical study to assess the toxicity of drugs used in the treatment of chronic myelogenous leukemia

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ABSTRACT— Chronic myeloid leukemia (CML) is an a myelopolifrative disorder characterized by the presence of an acquired mutation which affects the hematopoietic stem cell. Therefore, this study aims to investigate whether (imatinib or nilotinib) which are not harmful when used for long years. Theoretically, the Hyper Chem program was used to extract data (QSAR) to determine drug toxicity, which includes (Surface area, volume, Refractivity, Hydration energy, Partial charges, Polarizability, Mass, log P). And using this data in the PIC50 equation to extract to calculate the half - maximal inhibitory concentration (IC50). In the practical part. The analyzes that containing (GOT, GPT, GSH, and NF-KB), was used to analyze 35 sample patients were classified as receiving imatinib treatment and 35 sample patients were classified as receiving nilotinib treatment. We found in the drug imatinib the IC50 value was (1.258) the value was significantly lower than the value of nilotinib (3.732). A high proportion of (GOT, GPT, GSH, and NF-KB) was found in the group using nilotinib. It was proven that imatinib is an effective and safe treatment when used for many years.

KEYWORDS: CML, Imatinib, Nilotinib, IC50, GOT, GPT, GSH, NF-KB.

1. INTRODUCTION

Chronic myelogenous leukemia(CML) is considered one of the most common health diseases in the world, with a risk of infection increases with age. This disease is more common in men than among women, but the cause is unknown [1]. In Iraq, CML disease considered the fourth most frequent leukemia [2]. The development of treatment contributes to improving people with chronic myelogenous leukemia, and most patients reach the stage of recovery from symptoms and live for many years after diagnosis [3], [6]. Here in this study, we are trying to understand the toxicity of the drug used to treat in CML among different molecular response levels of CML patients undergoing imatinib and nilotinib therapy.

Theoretically

Quantitative structure-activity relationships (QSAR)

This method was necessary for drug discovery, structural properties refer to (physical and chemical) properties and biological activities consistent with pharmacokinetic properties such as toxicity, distribution, absorption, and excretion [3- 5]. QSAR modeling has served as an inevitable process in the pharmaceutical industry.

Table 1: QSAR properties for Imatinib and Nilotinib

Properties	Imatinib	Nilotinib
Surface area (Grid)	835.67	744.81
Volume	1452.28	1350.0
Refractivity	157.79	153.59
Hydration Energy (Kcal/mol)	8.98-	-10.34
Partial Charges	0.0	0.0
Polarizability	56.68	53.97
Mass(amu)	493.61	529.52
Log P	0.12	-0.51
Molar Weight	493.615	529.527

Calculation of PIC50

The value of PIC50 is estimated by using the equation (1) to derive QSAR property values shown in Table [1] using Hyper Chem 8.

PIC50 = 3.028 – 0.542 log p + 0.352 HE - 1.272 POL + 0.863 MR - 0.038 MV- 0.024 MW+19.120 q01 +0.024 SAG ……..(1)

Where

HE=Hydration Energy, Pol= Polazibility, MR= Molecular Refractivity

Log P = Partition Coefficient, MV = Molar Volume, MW = Molar Weight, SAG = Surface Area Grid, q01 = atomic net charges. [7].

Table [2]: Data of PIC50 of the Imatinib and Nilotinib

Properties	Imatinib	Nilotinib
PIC50	.90016	17.428

Half maximal inhibitory concentration (IC_{50})

It is a measure of a substance's effectiveness in inhibiting a specific biochemical or biological function. In pharmaceutical research, IC50 is used to measure the effectiveness of an antidote, as well as to measure the effectiveness of over-the-counter medications [8]. IC50 can be determined with competition-binding assays or with functional assays [9] The results in table (2) are substituted into Equation (2) to find the value of IC50.

$$\boldsymbol{PIC_{50} = -Log_{10}\,(IC_{50})} \qquad \ldots\ldots \qquad \mathbf{2}$$

Table 3: Data of IC50 of the Imatinib and Nilotinib

Molecular	Imatinib	Nilotinib
IC_{50}	1.258	3.732

We see from the table [3] that the imatinib molecule has the lowest value and then the nilotinib molecule has the highest value. A lower IC50 value indicates that the drug is effective at lower concentrations and will therefore exhibit less systemic toxicity when administered to the patient (8,9,10)

2. Methodology

2.1 Materials and methods

Subject: This study was conducted between Nov.2020_Apr.2021 at the National Center of Hematology in

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Baghdad, Iraq. Seventy-five patients with CML were enrolled in the present study, age >20 years old and on imatinib and nilotinib therapy for more than 1 year duration. Thirty –five patients were classified as receiving imatinib treatment and 35 patients were classified as receiving nilotinib treatment. Thirty samples without chronic disease or history of hematological were taken as a control group.

2.2 Blood analysis and biochemical measurements

Peripheral venous blood (5 ml) was collected in a gelatinous tube from CML cancer patients and from healthy control. The serum was separated after centrifuge at 1000 xg per minute for 10 min. Serum was stored at -20 ° C. Toxicity was determined an assay (ELISA) kit (glutamate- oxaloacetate transaminase, glutamic pyruvic transaminase, Glutathione, and nuclear factor kappa- light) (Mybiosource, USA)

2.3 Statistical analysis

Statistical analysis (One-way ANOVA) was performed using Graph Pad InStat Demo. The results were expressed as mean and standard deviation (mean ± SEM). A GOT, GPT, GSH, and NF-KB test was performed to analyze Statistical significance for both groups. P values 0.001 were considered statistically significant

3. Results

Content caused by dose Imatinib application as it shown in figure (1,2,3,4). Values are expressed as mean ± SEM.(n=5)***p< 0.001 shows significant difference 1 year first treatment when compared with control.###P< 0.001 shows difference in the 4year and 14 year when compared with 1 year. Consist of effect of Nilotinib on patient enzyme content caused by dose Nilotinib application as it shown in figure [5,6,7,8]. Values are expressed as mean ± SEM.(n=5)***p< 0.001 shows significant difference 1 year first treatment when compared with control.###P< 0.001 shows significant difference in the 3 year 6 year and 7 years when compared with control.

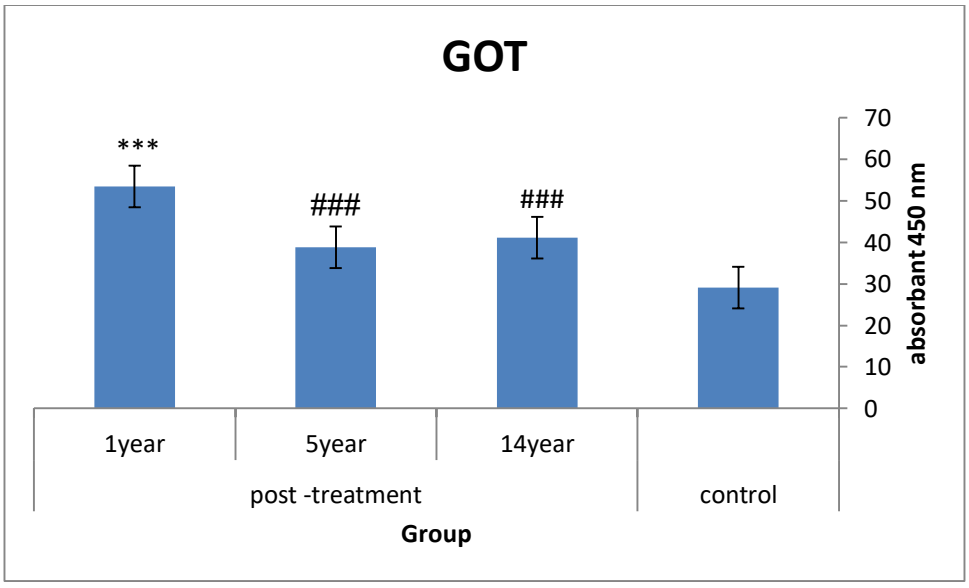

Figure 1. Effect of Imatinib on patients, GOT(glutamate- oxaloacetate transaminase)

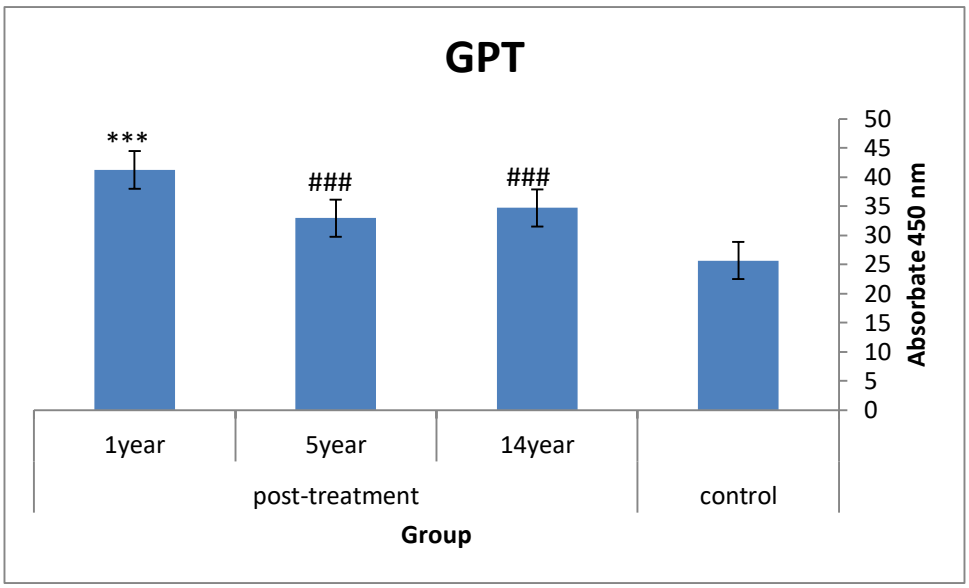

Figure 2. Effect of Imatinib on patients, GPT (glutamic pyruvic transaminase)

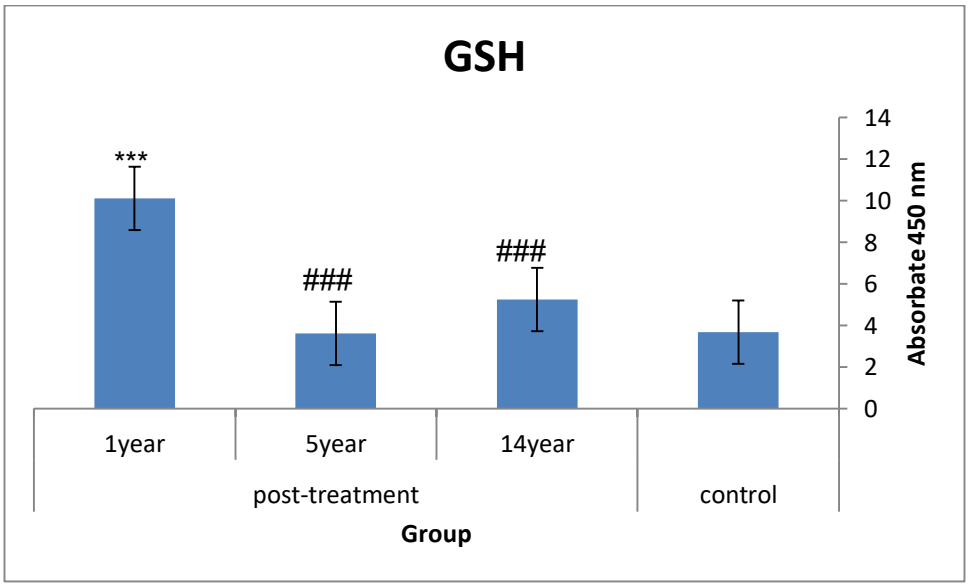

Figure 3. Effect of Imatinib on patients, GSH (Glutathione)

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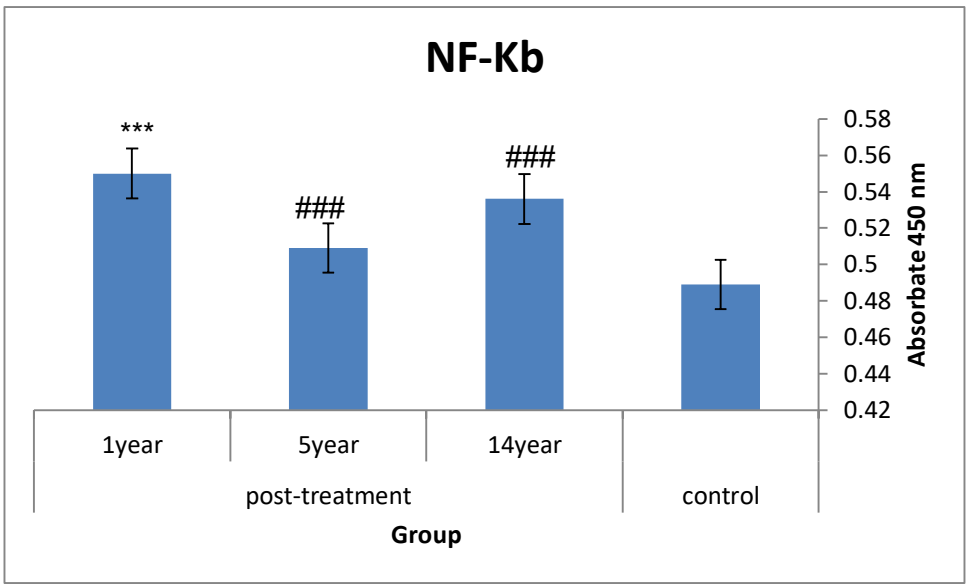

Figrue.4. Effect of Imatinib on patients (NF-κB) (nuclear factor kappa- light)

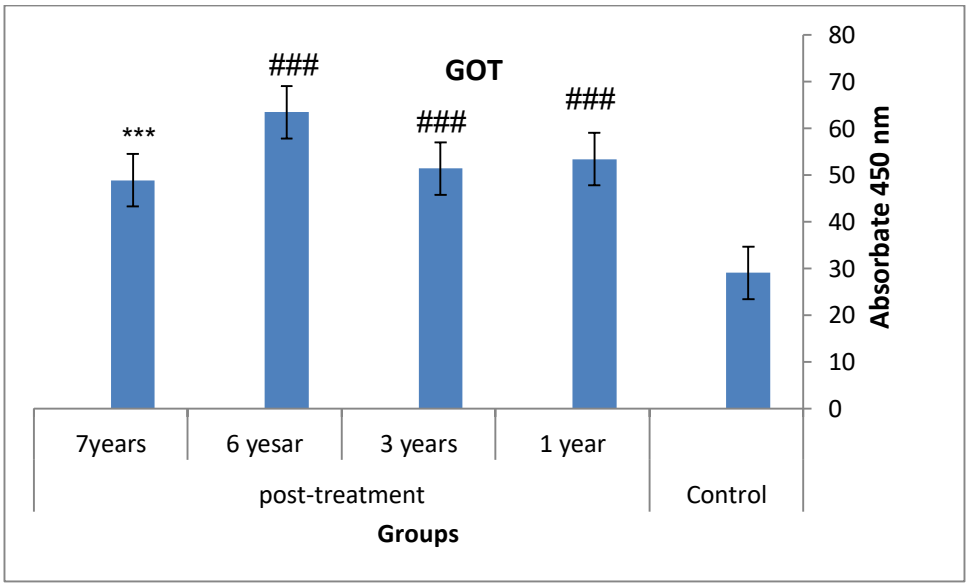

Figure 5. Effect of Nilotinib on patient, GOT (glutamate- oxaloacetate transaminase)

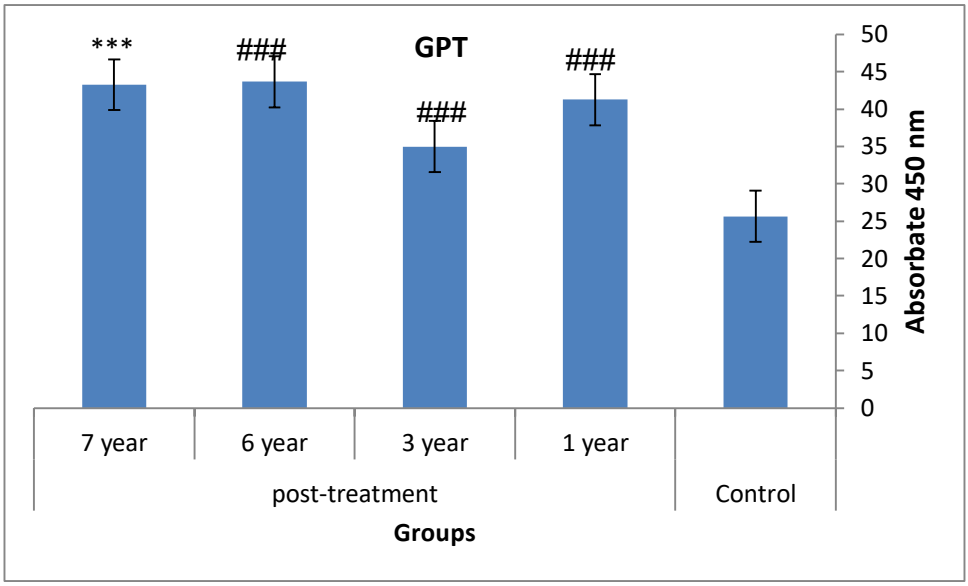

Figure 6. Effect of Nilotinib on patient, GPT(glutamic pyruvic transaminase)

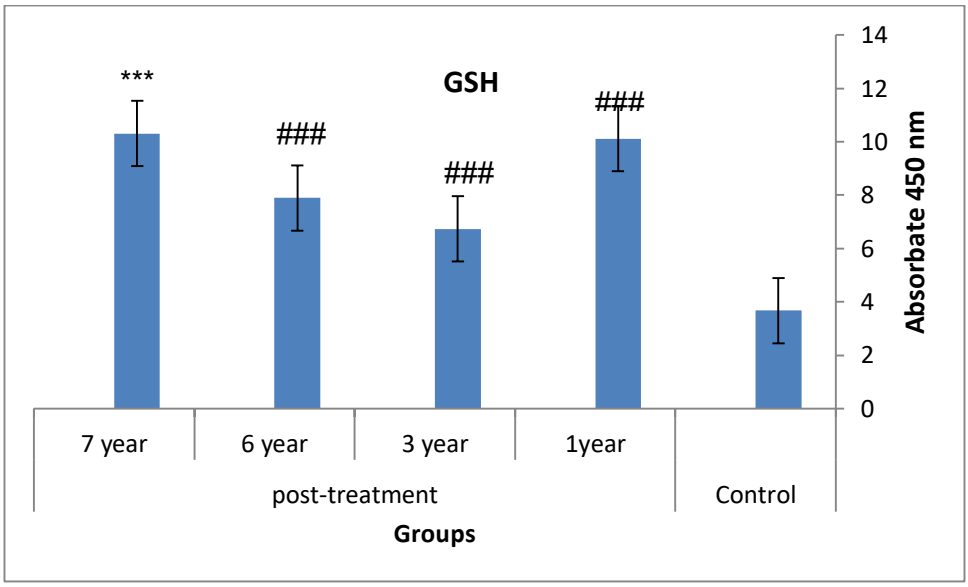

Figure 7. Effect of Nilotinib on patient, GSH (Glutathione)

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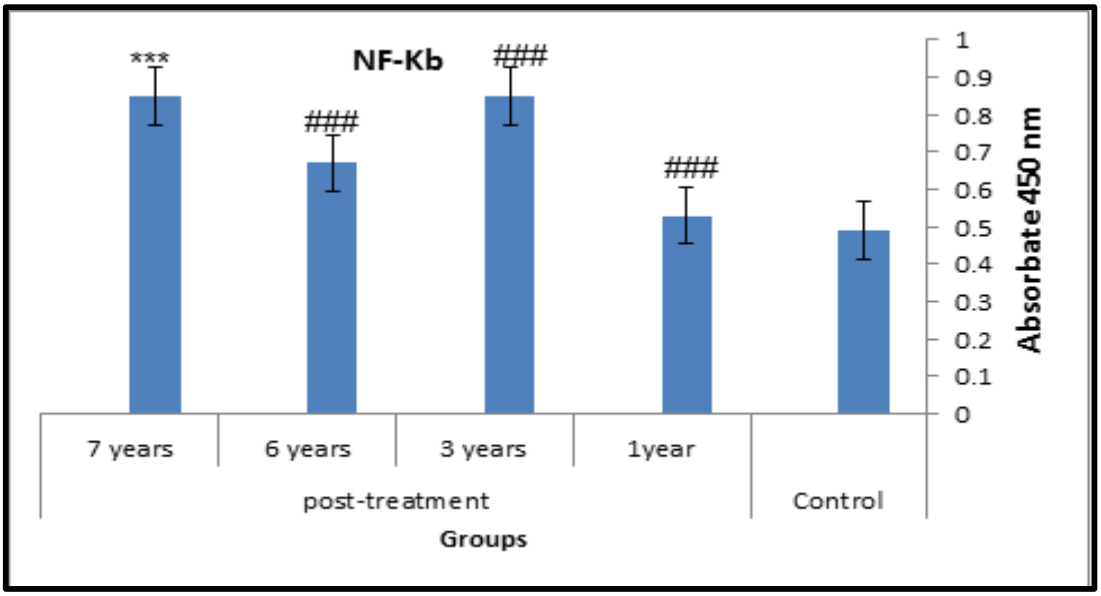

Figure 8. Effect of Nilotinib on patients (NF-κB) (nuclear factor kappa- light)

4. Discussion

The toxicity of drugs used in the treatment of chronic myelogenous leukemia has been theoretically studied. The drugs that have been used are imatinib and nioltinib. By using the Hyper-Chem program and extracting the IC50 value. The lower value means that the drug is effective, and this is what we found in the drug imatinib. The value was (1.258). The value was significantly lower than the value of nilotinib (3.732). These theoretical data were supported by analyzes (GOT,GPT, GSH, and NF-Kb) to demonstrate toxicity in practice.

As for the practical part, We note in figure (1) of Got and figure (2) GPT that when comparing control with the first year of using the treatment, there is a therapeutic response. Then after five years, there is an increase in the dose in the body, and after 14 years, there is a therapeutic response compared to five years, a slight significant change due to the body's adaptation to the specified dose. GSH: As shown in figure (3), it is thought to be one of the most important enzymes in the body in terms of toxicity [10]. In the first year of treatment, there was a therapeutic response compared to the control, and when the five years of treatment began to decrease because of the increase in the dose in the body. And at 14 years of treatment, when compared with five years, we note the defensive state began to increase because the patient continued the same treatment and continued to adapt to the body. The NF-KB is one of the indicators for stimulating inflammatory markers in a therapeutic response when comparing the first year of treatment with Control [11], [12]. We note that there is a slight difference when comparing 14 years with the first year of treatment. This indicates that the treatment is effective and non-toxic when used for many years. As shown in figure (4).

In figure (7) for the drug nilotinib we notice the GSH when comparing the first year of taking the treatment with control. It has a therapeutic response, but when comparing 7 years of treatment with the first year, we notice a lower response. In figure (8). We note that the indicator that sends signals for inflammatory or cancerous indicators is very high after 7 years, compared to 1 year. It implies that the more toxic the treatment is in the body, the higher the dose Hepatotoxicity is described as a liver injury associated with high liver function caused by imatinib drug exposure. In this work, we looked at the effects of imatinib on patient-induced activation of NF-kB and its downstream effectors, as well as the mechanism behind it.

Take, for example, enzyme function of life like GOT, GPT and GSH as show in figure (1,2,3) for the usage of imatinib, a well-known treatment that is widely utilized to comprehend the involvement of various intracellular agents and cascades in the promotion stage of cancer development. The current study shows that pos-treatment up-regulates NF-kB via suppressing oxidative stress, inflammatory responses, and cytokine production. As a result, imatinib prevents. While the nilotinib effect on patient leukemia infection causes high levels of certain liver enzymes (types of proteins), it can cause serious liver effects, including liver damage. Figure (8) shows that an enzymatic biomarker of inflammation also the NF-Kb irregular, was elevated indicating high toxicity compared to imatinib and greater safety than nilotinib.

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