Iraqi Journal of Cancer and Medical Genetics

Nilotinib effect on hepatic and renal functions in a sample of Iraqi patients with chronic myeloid leukemia

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Abstract:

Background: Chronic myelogenous leukemia is a clonal disorder of the pleuripotent stem cells which accounts for about 15% of leukemias. Tyrosine kinase inhibitors (TKIs) are the first line therapy for CML which have substantially improved the prognosis of CML. Nilotinib is a second generation TKI which is being used widely. as a frontline drug for CML treatment and also for imatinib resistant cases. Nilotinib has been reported to induce hepatotoxicity and to affect renal function
Objectives: The current study aims to evaluate the effect of nilotinib on liver and renal function in a sample of Iraqi patients with chronic myeloid leukaemia (chronic phase) treated with Nilotinib and its possible association with grades of other haematological parameters.
Patients and Methods: Thirty three patients with chronic myeloid leukaemia 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. Switching to Nilotinib treatment was due to intolerance or resistance to Imatinib. ALT, AST, blood urea, creatinine as well as other haematological parameters were measured.
Results: only one patient out of thirty three(3%) had a very high ALT and AST with grade 3 and only 2 patients (6%) were classified as grade 1 for ALT level. All the patients were within the normal range values of blood urea, creatinine and eGFR .
Conclusion: Hepatotoxicity is a serious adverse effect of nilotinib that mandates regular check-up of liver function.

Key words: *nilotinib, Chronic myeloid leukaemia, hepatotoxicity, renal dysfunction tyrosine kinase inhibitor*

Introduction:

Chronic myelogenous leukemia (CML) is a clonal disorder of the pleuripotent stem cells which accounts for about 15% of leukemias and is characterized by a slow progressive course that may eventually end in blastic phase that resemble an acute leukemia(1). The whole molecular characteristic of CML is the presence of Philadelphia chromosome which can be seen in more than 90% of patients(2). Philadelphia chromosome is the consequence of the t(9;22) (q34;q11) translocation between chromosomes 9 and 22 leading to the formation of the chimeric BCR□ABL1 gene(3) which codes for a fusion protein that has an enhanced tyrosine kinase activity(4).

The treatment of CML has been changed dramatically with the introduction of tyrosine kinase inhibitors (TKI) as a modality of treatment(5). These novel agents have changed this type of leukemia into a much more like a chronic disease that requires a long term therapy(6).

TKI can inhibit the enhanced tyrosine activity of the fusion protein by a mechanism based on interfering with binding of adenosine triphosphate (ATP)(7), blocking cellular proliferation of the malignant clone. Overall, TKI can improve the 10-year survival rate from approximately 20% to 80–90%(8).

The three commercially available TKIs for the treatment of CML include imatinib, dasatinib, and nilotinib and the current guidelines justify the use of them as frontline drugs in the treatment of chronic phase of CML(9).

Nilotinib (a second generation TKI) is an analogue to imatinib with higher affinity for the ATP binding sites in vitro(10). It can be used as a frontline drug for CML treatment and also for imatinib resistant cases(11). All these drugs have several side effects related to the inhibition of the other TKI.

Liver is the main site of metabolism of many therapeutic agents among which are many drugs used in the treatment of malignant diseases including leukemia. This process may lead to injury of hepatocyte resulting in elevation of liver enzymes(12). Many TKIs including nilotinib have been as-

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sociated with the incidence of hepatoxicity. It is now widely accepted that the mechanism by which TKIs induces hepatotoxicity is not related to their on-target effects –inhibiting tyrosine kinase- but rather other mechanisms are suggested including immune mediated (13), pharmacogenetic(14) and the role of intracellular signalling molecules such as VEGF(15) and c-jun kinase(16).

Most of these reports originated from the data of clinical trials performed for the approval of these drugs where patients are carefully selected in contrast to patients in every day practice(17) (18). Not too many reports have addressed the post marketing incidence of hepatotoxicity in patient with malignant diseases and even less to address this issue in CML patient because of the limited number of patients using these drugs and particularly nilotinib.

The effect of TKIs on renal function has been investigated in several studies-mostly case reports- but still information about this issue is scarce(19–21). The postulated mechanisms include tumor lysis syndrome and toxic tubular damage(22).

In the present study the association between the use of nilotinib in patients with CML and the incidence of hepatic and renal dysfunction has been investigated in a sample of Iraqi patients.

Patients and Methods:

Thirty three patients were enrolled in this cross sectional study, 19 females and 14 males with an age ranging from 30-70 years. All the patients enrolled were diagnosed as chronic myeloid leukaemia based on peripheral blood findings and molecular analysis for the BCR-ABL mutation by PCR. Patients with history of liver, renal or thyroid disease or already on treatment for thyroid dysfunction were excluded. Other exclusion criteria include: pregnancy, concomitant use of oral contraceptive pills or corticosteroids. The patients were on Nilotinib hydrochloride (Tasigna, Novartis) 400mg/d for six months. Switching to Nilotinib treatment was due to intolerance or resistance to Imatinib. The study was done at The National Centre for Haematological Diseases in Baghdad-Iraq from February-2016 to October 2016. The study also included a control group of 30 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 institutional ethics committee.

Patients on nilotinib were classified according to Common Terminology Criteria for Adverse Events (CTCAE) (23) regarding AST, ALT, blood urea creatinine and GFR.

Laboratory reference ranges for ALT, AST, urea, creatinine and eGFR are 7-14 U/L, 12-38 U/L, 7-20 mg/dL ,0.5-1 mg/dL and >90 mL/min/1.73m2 respectively.

Cobas C111 we used for biochemical tests. Samples were collected, processed, and analysed according to manufacture manual. Haematological parameters were measured using auto hematology analyzer (Mindray BC 3000,China).

All results are expressed as mean ±SD. SPSS statistical programme version 21 and Prism 6.01 have been used for data analysis and graphs development. Mann-Whitney test and chi-square statistical tests were used wherever appropriate.

Results:

Thirty three patients were enrolled in this study with a gender distribution of males and females of 14 (42%) and 19 (58%) respectively. The patient study group has a mean age around 54 years ranging from 30 to 70 years. A comparable group of subjects not taking nilotinib who are otherwise healthy were recruited as a control group who were matched both for gender and age as shown in table 1.

Table(1): patients characteristics

	Study group	Control group	
N	33	30	
Male	14 (42%)	14(46.6%)	
Female	19 (58%)	16(53.4%)	
Age(mean±SD) (range)	(53.9±11.7) (30-70)	(50.36 ±12.6) (20-72)	
ALT(mean±SD) (range)	(28.95±33.85) (10.9-209)	(19.8±6.3) U/L (7.8-37)	*p>0.05
AST(mean±SD) (range)	(27.18±36.2) (13.4-227)	(17.9±4.7) U/L (8-26)	*p<0.05
Blood urea(mean±SD) (range)	(26.9±5.12) (16.1-37.6)	(27.9±3.5) mg/dL (19.6±33.1)	*p>0.05
Creatinine(mean±SD) (range)	(0.7±0.11) (0.5-1)	(0.73±0.1) mg/dL (0.56-0.93)	*p>0.05

* Mann-Whitney U

The average means of both ALT and AST levels in the study group are within the normal limits, however the high standard deviations shown in table 1 is due to the presence of one patient with very high ALT and AST (209 and 227 U/L respectively) . For the control group, The means of both ALT and AST levels are within the normal limits but both are lower than that of the study group. Mann-Whitney test for comparison of two independent groups showed that there is a statistically significant difference between the study and the control groups regarding the AST level with the mean value being higher in the patients taking nilotinib (the study group). The same test showed also that there was no significant difference between the study and the control groups regarding the ALT level as shown in table 1.

Regarding the effect of nilotinib on the renal function as measured by blood urea, serum creatinine and eGFR, the average means of these parameters were within the normal limit or slightly elevated (blood urea) for both the study and control groups as shown in table 1. There was no significant difference between the study and the control groups regarding blood urea, cratinine or eGFR when Mann-Whitney test was used and as shown in table 1($p>0.05$).

Patients on nilotinib were classified according to Common Terminology Criteria for Adverse Events (CTCAE) regarding Hb, platelets , ANC AST, ALT, blood urea creatinine and eGFR.

As shown in figure (1), 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.

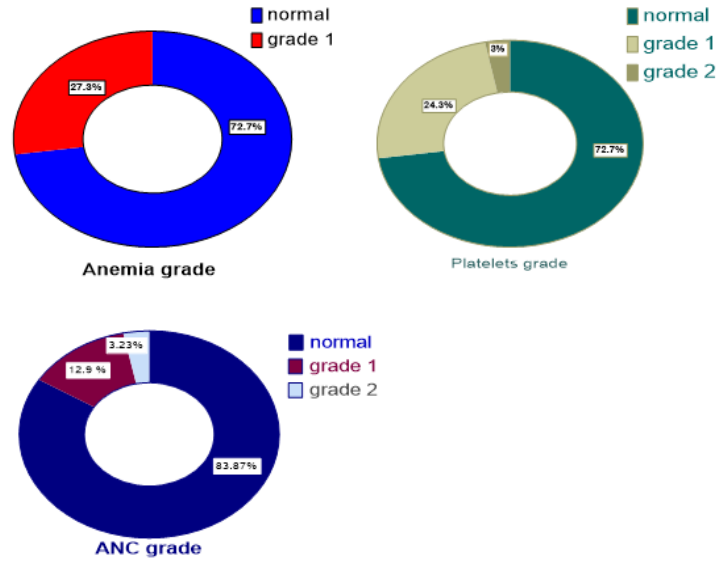

Figure (1): patients classified according to Common Terminology Criteria for Adverse Events(CTCAE) regarding Hb, platelets and ANC levels.

All the patients were within the normal range values of blood urea creatinine and eGFR so they were not classified with CTCAE. The vast majority of patients who were taking nilotinib have normal levels of ALT and AST. Only one patient has grade 3 for AST and ALT and three patients have grade 3 for ALT. all of the above results are schematically summarized in figure 2.

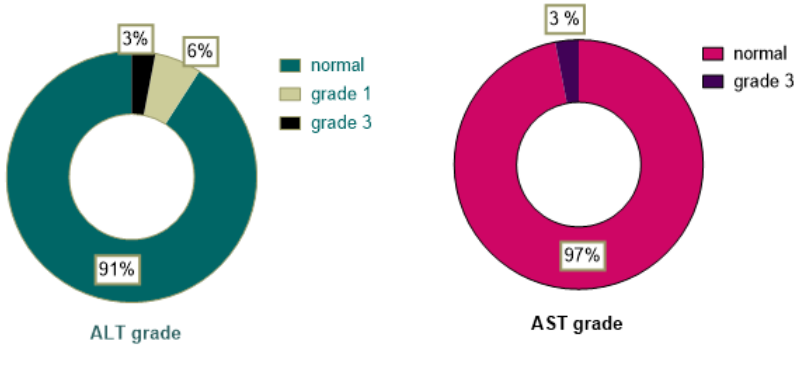

Figure (2): patients classified according to Common Terminology Criteria for Adverse Events (CTCAE) regarding AST, ALT.

The association between the CTAC grades of hematological parameters(Hb, platelets and ANC) and the grades of the renal and liver function parameters (blood urea, creatinine AST, and ALT) was assessed using Chi-square test and it was statistically non-significant.

Discussion:

Our study showed that only one patient out of thirty three(3%) had a very high ALT and AST levels (209 and 227 U/L respectively) which made him eligible to be classified in grade 3(severe) according to CTCAE(23). On the other hand only 2 patients (6%) were classified as grade 1(mild) for ALT level and the vast majority of patients were having normal levels of AST and ALT as shown in the results section. These results are consistent with other studies addressing the same subject. In one study(24), patients resistant to imatinib were assigned to take nilotinib where up to 4% of the patients having grade 3 of ALT and AST and whom were followed for duration of four months. In another study with follow up of 24 months(25) with same dose as in our study, 3% of patients had grade 3 for AST and about 9% had grade 3 for ALT. these finding are similar to ours regarding AST but differ for the ALT probably due to the longer period of follow up. In one study in Japanese patients(26)with follow up of 36 months, none of the patients had grade 3 or more, rather less than one fifth of them had milder grades. This finding might be attributed to the small sample size (only 16 patients in chronic phase) but might also suggest that different ethnic populations may have different reactions to nilotinib.

Nilotinib beside other TKIs has the potential to inhibit one of the isoenzyme responsible for the glucouronidation of acetaminophen which will be metabolized by an alternative pathway that ends in hepatoxic compound (27) . This proposed mechanism of enhanced hepatoxicity led to the recommendation of the caution upon use of high dose imatinib with acetaminophen(28) and whether the same is true for nilotinib remains to be answered.

Regarding the effect of nilotinib on renal function, All the patients were within the normal range values of blood urea, creatinine and eGFR. The effect of TKIs on renal function has been investigated in several studiesand mostly of them are case reports (19–21). In one recent study (29), CML patients in the chronic phase treated with different TKIs including nilotinib were evaluated for renal function. Out of 116 patients treated with nilotinib only 2 patients had mild increase in creatinine level and none of them had abnormal eGFR. Considering the larger sample size compared to our study and the longer period of follow up, might explain the discrepancy from our findings.

In conclusion, hepatotoxicity is a serious adverse effect of nilotinib that mandates regular check-up of liver function as recommended by the FDA regulation. Due to lacking studies that address the effect of TKIs on the hepatic and renal function, our study can be seen as window to look at that subject in Iraqi population.

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تأثير عقار نيلوتنب على وظائف الكبد والكلى لنموذج من المرضى العراقيين المصابين بأبيضاض الدم الحبيبي المزمن

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الخلاصه:

يعتبر ابيضاض الدم الحبيبي المزمن مرض يصيب الخلايا الجذعية ويشكل 15% من جميع حالات ابيضاض الدم. تعتبر مثبطات التايروسين كاينيز Tyrosin kinase)) الخط الاول لعلاج ابيضاض الدم الحبيبي المزمن والذي أدى الى تحسن حالة المرضى.

يعد نيلوتنب الجيل الثاني من مثبطات التايروسين كاينيز والذي يتم استخدامه على نطاق واسع لعلاج مرضى ابيضاض الدم الحبيبي المزمن وكذلك الحالات المعندة لعلاج ايماتنب. لعقار نيلوتنب تأثيرات جانبية على وظائف الكلى والكبد.

تهدف الدراسة الى تقييم تأثير نيلوتنب على وظائف الكبد والكلى لبعض المرضى العراقيين المصابين بابيضاض الدم الحبيبي مع علاقة ذلك بدرجات التأثير على المؤشرات الدموية.

المرضى وطريقة العمل تضمنت الدراسة ثلاثة وثلاثون مريضا بابيضاض الدم المزمن الحبيبي مع نفس العدد من الاصحاء كمجموعة السيطرة. جميع المرضى يتعاطون نيلوتنب لمدة 6 اشهر على الاقل. التغيير من ايماتنب هو اما بسبب عدم تحمل المريض لعلاج ايماتنب او مقاومة المرض للعلاج. يتم عمل انزيمات الكبد (ALT & AST) ونسبة اليوريا والكرياتنين في الدم والمؤشرات الدموية الممكنة.

اظهرت النتائج وجود مريض واحد فقط من ثلاثة وثلاثون مريض (3%) لديه ارتفاع عالي في انزيمي(ALT & AST) ويقدر بدرجة (3) ومريضين يصنفون كدرجة اولى لارتفاع مستوى الانزيم ALT . كل المرضى لديهم اليوريا والكرياتنين في الدم ضمن الحدود الطبيعية, وكذلك معدل ترشيح الانيبوبات (GFR) .

الاستنتاج تسمم الكبد يعتبر تأثير جانبي خطر لعقار نيلوتنب والذي يتضمن مراقبة المريض بواسطة اجراء فحوصات ووظائف الكبد بشكل دوري.