

Evaluation of Electrolytes Disturbances in Iraqi Chronic Myeloid Leukemia Patients treated with Nilotinib with Monitoring of Response by FISH Study

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Abstract:

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the presence Philadelphia chromosome (Ph) which was created by a reciprocal translocation between chromosomes 9 and 22 (t [9;22] [q34;q11]). The approval of the 2nd generation TKI (Nilotinib) takes the treatment of CML patients into new era with more efficiency and mild to moderate adverse effects. This study was aimed at evaluation of molecular cytogenetic response by (FISH) for Nilotinib in Iraqi patients with assessment for electrolytes disturbances of Nilotinib by measuring a panel of electrolyte (Na⁺, K⁺, Ca⁺⁺, PO₄⁻⁻⁻ and Mg⁺⁺) , where thirty Iraqi patients with CML who have resistance or no response to Imatinib treatment, attending to Baghdad Teaching Hospital/Hematology Department, have been submitted to this study. Blood samples have been taken pre and post starting treatment with Nilotinib, FISH study was done only for CML patients, while 30 normal healthy control volunteers submitted to the same panel of electrolytes measurements (Na⁺, K⁺, Ca⁺⁺, PO₄⁻⁻⁻ and Mg⁺⁺) in addition to pre and post treatment Nilotinib patients.

The results show out of 30 patients (17) males and (13) females with male to female ratio 1.3:1, FISH results for patients (pre and post) treatment mean±SD were(58.7%±26.2 % and 45.7%±29.9%) obviously significant with good cytogenetic response in resistance CML for Imatinib. Sodium levels in mmol/L pre, post treatment and control mean±SD were (139.2±6.9 , 142.4±9.2 and 140.4±2.52) respectively, with no significant difference between each other with P value > 0.05 in all comparisons. Potassium levels mean±SD in mmol/L results for patients (pre, post) and control were (4.6±0.69, 4.3±0.68 and 4.46±0.76) respectively, with no significant difference between each other with P value > 0.05 in all comparisons. Calcium levels in mg/dL results for patients (pre, post) and control as mean±SD were (8.68 ±1.68, 8.1±1.72 and 9.12±0.38) respectively with no significant differences except between post treatment and control group with P value > 0.05 in all comparisons. Phosphate levels in mg/dL results for patients (pre, post) and control as mean±SD were (2.5±0.84, 2.95±1.04 and 3.4±0.49) respectively with significant difference with P value < 0.05 in all comparisons. Magnesium levels in mg/dL results for patients pre, post and control as mean±SD were (1.93±0.34, 2.06±0.44 and 2.1±0.34) respectively with no significant difference between each other with P value > 0.05 in all comparisons. This study sheds a light on the molecular cytogenetic response for CML patients who have already resistance to Imatinib and Nilotinib that has much more potent effect as approved by studies and this study has used FISH technique. This study emphasizes on the importance of evaluation of electrolyte panel for CML patients before starting Nilotinib study taking in to consideration if these patients are

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already receiving Imatinib which can also affect bone metabolism and calcium and phosphate levels.

Key words: Chronic myeloid leukemia(CML), Fluorescent in situ hybridization(FISH)

Introduction:

Chronic myeloid leukemia (CML) is a myeloproliferative disorder that is a consequence of an acquired mutation affecting hematopoietic stem cells. This mutation results in a balanced translocation between chromosomes 9 and 22, initially identified in 1960, and termed the Ph chromosome [t(9;22)(q34;q11)][1].

Chronic myeloid leukemia occurs more frequently in adults than in children. It occurs at roughly the same frequency in countries around the world and is no more common in one ethnic or racial group than in any other. The annual incidence rate is 1.6 cases per 100,000 adults (approximately 5000 new cases per year in the United States), with a male-to-female ratio of 1.4 to 1[2]. The median age at diagnosis is approximately 55 years, with less than 10% of patients under the age of 20 years[3].

CML normally progresses through three clinically recognized phases about 90% of patients are diagnosed during the typically indolent chronic phase (CP), which is followed by an accelerated phase (AP) and a terminal blastic phase (BP), 20-25% of patients progress directly from CP to BP and the time course for progression can be extremely varied [4]. In all patients with chronic phase CML, the disease has the potential to evolve into a more aggressive, more symptomatic, and troublesome phase, which is poorly responsive to the therapy that formerly controlled the chronic phase. The failure of therapy to restore or maintain near-normal red cell and white cell counts, increased spleen size, increased numbers of marrow

blasts and blood basophils, loss of the sense of well-being, and appearance of extramedullary tumors are the most consistent clinical hallmarks of the metamorphosis of the chronic to the accelerated phase of CML[5,6].

Fluorescence in situ hybridization

(FISH):- is a rapid diagnostic test using molecular cytogenetic techniques. The FISH technique supplements conventional cytogenetic and in some cases provides additional information, which is not detected by karyotyping. A large number of cells can be studied by FISH, since interphase nuclei can also be analyzed [7]. FISH technique performed on interphase cells from both peripheral blood (PB) and bone marrow[8]. This helps in the detection of minimal residual disease, assessment of the rate of cytogenetic remission and detection of disease recurrence [9].

FISH detects BCR-ABL in about 95% of CML cases. It is the most sensitive test for diagnosis because it detects the approximately 5% of cases with "masked" translocations that are missed by cytogenetics [10], and it also detects rare cases with variant breakpoints falling outside the regions covered by PCR primers FISH has several advantages over cytogenetic. The specificity of the newer split signal assay is high. Also, unlike cytogenetic, which requires dividing metaphase cells, FISH can be performed on interphase nuclei in peripheral blood. It therefore may bypass the requirement for a bone marrow specimen. However, the percentage of BCR-ABL positive nuclei determined by FISH using peripheral blood specimens

seems to be lower than that using bone marrow.[11]

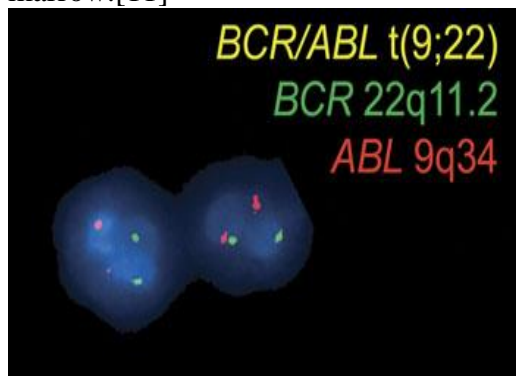


Fig. (1):The FISH strategy to detect the t(9;22) uses 2 differently labeled probes. A normal interphase nucleus (left) reveals 4 separate signals, 2 for each allele of *BCR* (green) and *ABL* (red). The appearance of a red-green fusion signal (nucleus to right) indicates the presence of *BCR-ABL* and is diagnostic of CML (4,6-diamidino-2-phenylindole-dihydrochloride nuclear counterstain, $\times 100$). Courtesy of A. Roy, Department of Pathology, Brigham and Women's Hospita

The first tyrosine kinase inhibitor for CML, imatinib mesylate was a major breakthrough in CML treatment, After 6 years of treatment, the overall survival (OS) was 88% [12]. Resistance to imatinib occurs annually in 3% to 4% of patients with CML in chronic phase (CML-CP), and is defined as failure to achieve complete hematologic response (CHR) within 3 months of therapy, any cytogenetic response within 6 months, or major cytogenetic response ($\text{Ph}^+ \leq 35\%$) within 12 months, or the development of cytogenetic or hematologic relapse [13]. Resistance can be mediated through BCR-ABL-dependent mechanisms, often through mutations in the ABL kinase domain (40%–50%), or by mechanisms independent of BCR-ABL[14]. Nilotinib (Tasigna®) a second generation TKI derived from imatinib, is a selective Abl

inhibitor that binds to the inactive/closed conformation of the Abl kinase that also inhibits c-KIT, ARG, PDGF α and PDGF β . Nilotinib was approved in 2007 for treatment of CML patients with resistance or intolerance to imatinib and was in 2010 approved for newly diagnosed patients[15] The cumulative rates of MMR (major molecular remission) by 3 years was 70% to 73% with nilotinib (two different doses) and 53% with imatinib, combined with a significantly lower rate of transformation to AP or BP was observed, 2.1-3.2% vs 6.7%, respectively[16].

Nilotinib can cause several side effects which varies from mild to moderate side effect (QT prolongation, sudden death, myelosuppression, elevated serum lipase, hepatotoxicity and electrolyte disturbances). The use of Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcaemia, hypomagnesemia, and hyponatremia. Electrolyte abnormalities must be corrected prior to initiating Tasigna and these electrolytes should be monitored periodically during therapy[17].

Subjects, Materials and Methods:-

This study was conducted between December 2012up to May2013; during this period 30 Iraqi patients of chronic myeloid leukemia treated with imatinb who failed to achieve cytogenetic response for various duration of treatment where the physician decided to go for the second generation of TKI (Nilotinb) were submitted for this study at Baghdad Teaching Hospital/Hematology Department. Laboratory tests including complete blood picture and fluorescent *in situ* hybridization for BCR-ABL conducted in Lab. Of Hematology and Immunology while the electrolytes

(Na⁺, K⁺, Ca⁺⁺, PO₄⁻⁻⁻ and Mg⁺⁺) conducted in Al-Nadhir Lab. Results were considered in our evaluation before starting treatment with Nilotinib and after two months from the start of the treatment. FISH study done using heprinized blood samples from the patients pre and after treatment using the interphase FISH technique. Electrolyte assay (potassium and sodium) carried out by using ISE (ion selective electrode), for phosphate, calcium and magnesium the assay done by Cobas C311 chemistry analyzer photometrical measurement, and both

instruments (ISE analyzer and Cobas C311) from Roche.

Result:

The data obtained from the CML patients before starting treatment with Nilotinib where all of them have no response to Glivec or develop resistance to glivec these results for (Ca, Na, K, Mg and PO₄ in addition to FISH study results) compared once with control healthy group and another time compared with the results of the same patients after starting the treatment with Nilotinib.

Table (1) FISH results statistics for pre and post treatment

	Pre treatment				After treatment				P value
	Mean	N	±SD	Median	Mean	N	±SD	Median	
FISH	58.7%	30	26.2%	62.0%	45.7%	30	29.9%	5.56%	.000

Table (2) The tabel shows the mean,SD,median, and P value for (Ca,Na,K,Mg,PO₄)befor treatment compared with healthy control group.

	Pre treatment				Control group				P value
	Mean	N	±SD	Median	Mean	N	±SD	Median	
Ca⁺⁺ (mg/dL)	8.69	30	1.68	8.81	9.12	30	.38	8.97	.223
PO₄⁻⁻⁻ (mg/dL)	2.51	30	.84	2.40	3.43	30	.49	3.44	.001
Na⁺ (mmol/L)	139.21	30	6.91	139.00	140.42	30	2.51	140.50	.420
K⁺ (mmol/L)	4.63	30	.70	4.50	4.46	30	.76	4.30	.393
Mg⁺⁺(mg/dL)	1.93	30	.342	1.95	2.10	30	.342	2.01	.017

Table (3) The tabel shows the mean,SD,median, and P value for(Ca,Na,K,Mg,PO₄) after treatment compared with healthy control group.

	After treatment				Control group				P value
	Mean	N	±SD	Median	Mean	N	±SD	Median	
Ca⁺⁺ (mg/dL)	8.1	30	1.72	8.8100	9.12	30	0.38	8.975	0.004
PO₄⁻⁻⁻ (mg/dL)	2.95	30	1.04	2.4	3.43	30	0.49	3.4	0.033
Na⁺ (mmol/L)	142.41	30	9.24	140.0	140.42	30	2.52	140.5	0.273
K⁺ (mmol/L)	4.33	30	0.68	4.3	4.46	30	0.76	4.3	0.539
Mg⁺⁺(mg/dL)	2.07	30	0.45	1.95	2.11	30	0.1	2.01	0.634

Table (4) The tabel shows the mean, SD, median, and P value for (Ca, Na, K, Mg, PO₄) pretreatment compared with post treatment.

	Pre treatment				After treatment				P value
	Mean	N	±SD	Median	Mean	N	±SD	Median	
Ca⁺⁺ (mg/dL)	8.69	30	1.68542	8.8100	8.10	30	1.72257	8.5900	.156
PO₄⁻⁻⁻ (mg/dL)	2.51	30	.83698	2.4000	2.95	30	1.04223	2.7600	.018
Na⁺ (mmol/L)	139.21	30	6.910	139.00	142.41	30	9.241	140.00	.144
K⁺ (mmol/L)	4.63	30	.6980	4.500	4.33	30	.6810	4.300	.092
Mg⁺⁺(mg/dL)	1.93	30	.34240	1.9500	2.07	30	.44564	1.8000	.183

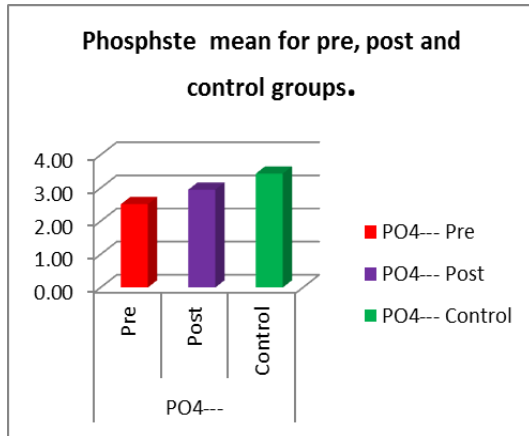


Fig. (2)

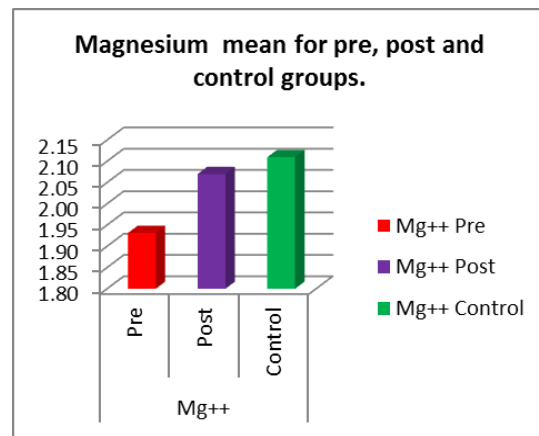


Fig.(3)

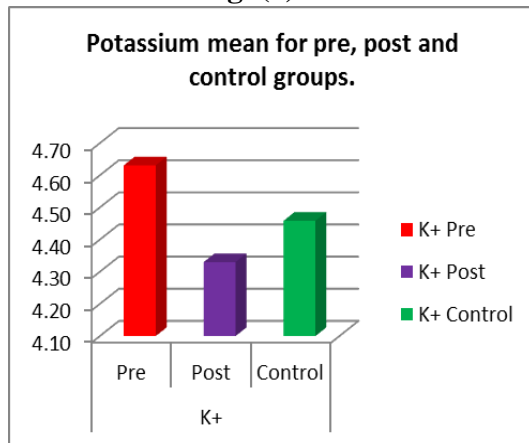


Fig. (4)

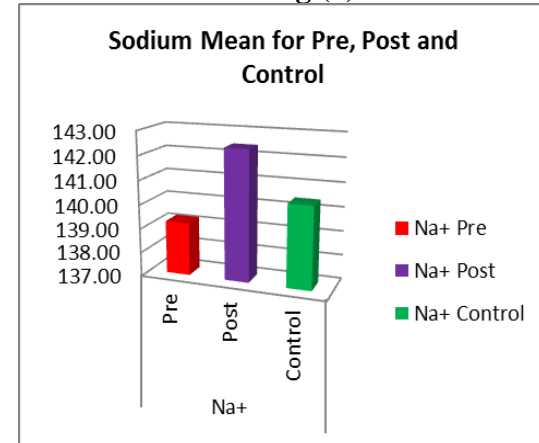


Fig. (5)

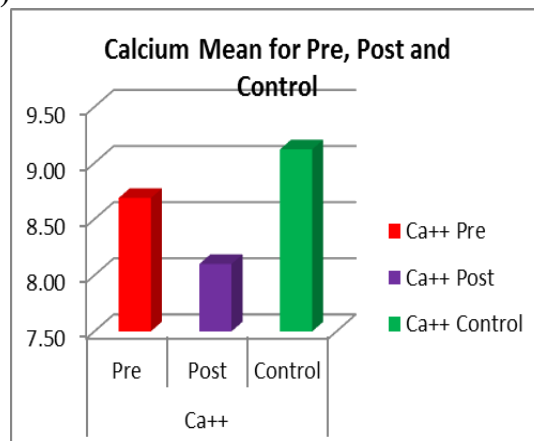


Fig. (6)

Figures above (2,3,4,5 and 6) represent the pre, Post treatment and control Mean levels comparison for PO_4^{--} , Mg^{++} , K^+ , Na^+ & Ca^{++} respectively.

Discussion:

FISH results comparison between pre and post treatment group showed significant decrease in BCR- ABL carrying cells percentage which agrees with studies of Mauro(2009)[18] study, Hazarika and Kantarjian studies(2008)[19,20], taking in

consideration the interval between pre and post treatment sampling where in the mentioned studies 6 months while in this study it was 1-3 months.

Regarding Sodium, Potassium and Magnesium there was no significant difference in all comparisons between pre, post and control groups which also

agrees with the studies of Nilotinib prescribing information and with Hughes TP, et al.(2012)[21] study, although more patients enrolled in the previous studies (more than 100) but the results of this study agree with the previous two studies.

Phosphate results for pre, post and control groups shows significant difference in phosphate levels for all comparisons where there was significant decrease of phosphate levels for both pre and post treatment groups in comparison with control group, there was also significant difference between pre and post treatment group where the last one shows higher levels which can be attributed to previous effect of Glivec at these patients because Imatinib has more adverse effect on phosphate and calcium because it had been observed to cause hypophosphatemia and hypocalcemia due to altered bone and mineral metabolism.[22,23,24,25]

These results for phosphate level also agree with ENEST trial study (2012)[26] and with Hughes TP, et al.(2012) study showed that the number was more than of patients who have hypophosphatemia in Imatinib group which is opposite to pretreatment group in this study in comparison with patients receiving Nilotinib which agrees with our results. Regarding Calcium there was no significant difference in all comparison except for that between post treatment group and control , agreed with Tasigan prescribing information by (Novartis) that was in two different studies 321 CML patients who were enrolled in one study and 137 CML patients who were in another study whose percent of hypocalcemia was 2 and 5 % respectively[26].

Conclusion:

This study sheds a light on the molecular cytogenetic response for CML patients who have already resistance to Imatinib and Nilotinib that has much more potent effect as approved by studies and this study has used FISH technique.

This study emphasizes on the importance of evaluation of electrolyte panel for CML patients before starting Nilotinib study taking in to consideration if these patients are already receiving Imatinib which can also affect bone metabolism and calcium and phosphate levels.

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تقييم اضطرابات الأملاح للمرضى العراقيين المصابين بأبيضاض الدم النقياني المزمن المصاحبة لعقار النيلوتنوب والاستجابة بواسطة تقنية التهجين الموضعي الوماض

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الخلاصة:

أبيضاض الدم النقياني المزمن (CML) هو اضطراب يتميز بوجود كروموسوم فيلادلفيا (Ph) والذي ينشأ من الانتقال المتبادل بين كروموسوم 9 و 22 [q34;q11] [t(9;2)]. وتطوير العقاقير المثبطة للتايروسين كايينز الذي يستهدف BCR-ABL يمثل نقلة نوعية في علاج أبيضاض الدم النقياني المزمن. ان استعمال الجيل الثاني من الأدوية المثبطة للتايروسين كايينز نييلوتنوب اثبت انتقال مرض ابيضاض الدم النقياني المزمن الى مرحلة جديدة من العلاج الكفوء مع اعراض جانبية عكسية طفيفة الى متوسطة. وهدفت الدراسة الى تقييم التأثير الأيضي لعقار النيلوتنوب Nilotinib من خلال دراسة الاستجابة الجزيئية الخلوية باستخدام تقنية I-FISH. مصحوبة بقياس تراكيز مجموعة من الأملاح في الجسم (صوديوم، بوتاسيوم، كالسيوم، فوسفات والمغنيسيوم). حيث تم اخضاع 30 مريض عراقي مصاب بأبيضاض الدم النقياني المزمن لديهم مقاومة او عدم استجابة لعقار الأيماتنوب في مستشفى بغداد التعليمي خضعوا لهذه الدراسة بأخذ عينات دم لهم قبل وبعد الشروع بأخذ عقار النيلوتنوب، وتم أيضاً اخذ 30 شخص سليم متطوع مجموعة السيطرة. حيث تم قياس نفس الأملاح لهم (صوديوم، بوتاسيوم، كالسيوم، فوسفات و مغنيسيوم) ماعدا دراسة ال I-FISH انجزت فقط لمرضى ابيضاض الدم النقياني.

حيث اظهرت النتائج من اصل ثلاثون مريضاً عراقياً هناك (17 ذكور و 13 اناث)، نسبة الذكر الى الأنثى 1.3:1 وكانت النتائج كالاتي:-

فيما يتعلق بنتائج ال (FISH study) كانت (45.7%±29.9% and 58.7%±26.2%) بعد وقبل البدء بعلاج النيلوتنوب وشهدت فرقا معنوياً حيث ان ال P value أصغر من 0.05. أما بالنسبة لمجموعة الفلزات التي تم راستها كانت النتائج كالاتي:

1- كان متوسط المستوى لفلز الصوديوم (mmol/L) قبل وبعد البدء بأستعمال عقار النيلوتنوب ولمجموعة المرضى والسيطرة (142.4±9.2، 139.2±6.9 و 140.4±2.52) على التوالي وبدون اي فرق احصائي بين هذه المجاميع حيث ان P Value أكبر من 0.05.

2- كان متوسط المستوى لفلز البوتاسيوم (mmo/L) قبل وبعد البدء بأستعمال عقار النيلوتنوب ولمجموعة المرضى والسيطرة هي (4.3±0.68، 4.6±0.69 و 4.46±0.76) على التوالي وبدون اي فرق معنوي بين هذه المجاميع حيث ان P Value أكبر من 0.05.

3- كان متوسط المستوى لفلز الكالسيوم (mg/dL) قبل وبعد البدء بأستعمال عقار النيلوتنوب ولمجموعة المرضى السيطرة هو (8.1±1.72، 8.68 ±1.68 و 9.12±0.38) على التوالي ولم يشهد اي فروقات معنوية بين هذه المجاميع الثلاثة ماعد المقارنة بين مجموعة السيطرة ومجموعة مابعد العلاج حيث كان ال P value للمجموعة الأخيرة هو 0.004.

4- كان متوسط المستوى لفلز الفوسفات (mg/dL) قبل وبعد البدء بأستعمال عقار النيلوتنوب و لمجموعة المرضى والسيطرة هو (2.95±1.04، 2.5±0.84 و 3.4±0.49) على التوالي وكان هناك فروقات معنوية بين المجاميع عند مقارنة كل واحد مع الآخر حيث ان ال P value أصغر من 0.05.

5- كان متوسط المستوى لفلز المغنيسيوم (2.06±0.44، 1.93±0.34 و 2.1±0.34) قبل وبعد البدء بأستعمال عقار النيلوتنوب ولمجموعة السيطرة ولم تظهر اي فروقات معنوية عند مقارنة احدهما مع الآخر حيث كان P value اكبر من 0.05 .

وخلصت هذه الدراسة على تأكيد اهمية تقييم مجموعة الفلزات لدى مرضى ابيضاض الدم النقياني قبل وبعد الشروع بعقار النيلوتنوب مع الأخذ بنظر الاعتبار أن المرضى الذين خضعوا لهذه الدراسة كانوا يستعملون عقار الأيماتنوب والذي من الممكن ان يؤثر على أيض ملح الكالسيوم والفوسفات في العظام. وأيضاً تلقي ضوء على الاستجابة الخلوية الجزيئية وخاصة انهم كانوا يعانون من فقدان الاستجابة لعقار الأيماتنوب وتظهر القوة تأثير النيلوتنوب وهذا يؤكد نتائج الدراسات الأخرى.