



Effect of Tyrosine Kinase Inhibitor in Patients with Chronic Myeloid Leukemia (Cytogenetic, Molecular response) in Mosul-Iraq

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Abstract

Objective: To evaluate the cytogenetic, molecular response, effect particularly on bone and heart for imatinib and nilotinib respectively in patients with chronic myeloid leukemia.

Methods: the study was conducted on eighty seven patients on imatinib and twenty nine patients on nilotinib as second line treatment who were treated at Ibn-sena teaching hospital /outpatient hematology department were reviewed from April 2002 to April 2014. Eligible patients were 18 years or older, mean age 41.17 year (range 18-75 year), 42 male and 45 female all are in chronic phase CML. The 29 patients on nilotinib, of them 16 were male and 13 were female mean age 43 year (range 25-70 years) initially treated by imatinib and switched to nilotinib due to primary, secondary failure or drug intolerance. The FISH analysis was carried on at central authorized laboratory in Baghdad. The RT-PCR carried on authorized laboratory initially in Baghdad then in Mosul, (both laboratory using the same standard and sponsored by Novartis). To study the effect of imatinib mesylate on bone mineral density fifty out of 87 patients were enrolled for this purpose. For all the patients ionized calcium, total calcium, serum albumin, and serum alkaline phosphatase, serum phosphate, and urea, creatinine and serum levels of intact parathyroid hormone measured at baseline, 6 months and 12 months. Dual Energy X-ray Absorptiometry (DEXA) measurements of the lumbar spine (L2–L4 vertebrae), and femoral neck were performed using a DEXA scanner.

For the nilotinib group, all patients had a base-line standard 12-lead Electrocardiography (ECG), with a follow-up ECG's performed every 6 months during the study period to assess any occurrence of QT prolongation, ischemic changes, or arrhythmias. Noninvasive cardiac imaging was performed using the resting transthoracic Echocardiography (Echo) with its 2-dimentional and M-mode views.

Results: The median duration of CML is 8 years (range 4-12) and the median duration of treatment by the first generation of the brand tyrosine kinase inhibitor is 8 years (range 4-12). Of the 87 patients who were eligible for follow up 86 (98.8%) achieved complete and major cytogenetic response and 86.21% have complete and major molecular response. For those on nilotinib 68.94% have complete and major cytogenetic and molecular response. The overall survival rate is 86.20% at 12 year of imatinib therapy. The 5 years survival rate after nilotinib treatment is 68.94% (20 out of 29). DEXA analysis revealed no significant changes in L2–L4 lumbar vertebral Bone Mineral Density (BMD) but there is significant change at femoral neck.

Prolongation of QTcF was observed in 80% of patients on nilotinib with a mean of 13.56 milli second. There were no significant difference in left ventricular ejection fraction % from the baseline and none of the patient develop major cardiac event.

Conclusion: Complete and major molecular response is 86.20% on imatinib therapy where as it is 68.94% on nilotinib as second line therapy. The overall survival rate is 86.20% at 12 year of imatinib therapy. The 5 years survival rate after nilotinib treatment is 68.94%. Significant decrease in femoral neck Bone Mineral Density (BMD) observed after 12 month time point. Nilotinib prolonged the QTcF interval by an average of 13.56 milli second with no adverse cardiac events.

Introduction

Chronic myeloid leukemia is a clonal myeloproliferative disorder characterized by the presence of Philadelphia chromosome which represent, a translocation between chromosome 9 and 22, and its product BCR-ABL1 transcript which has been shown to contribute to growth

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Received Date: 20 Sep 2018

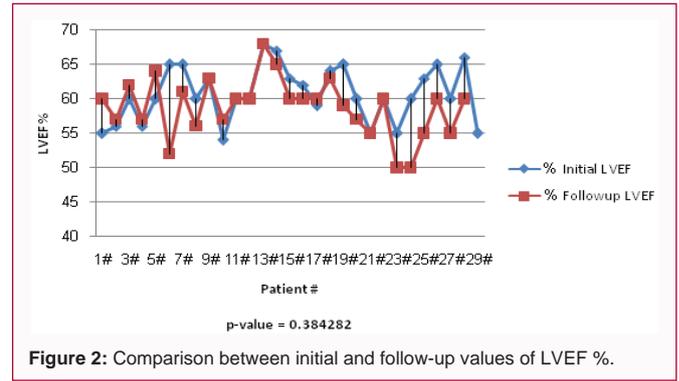
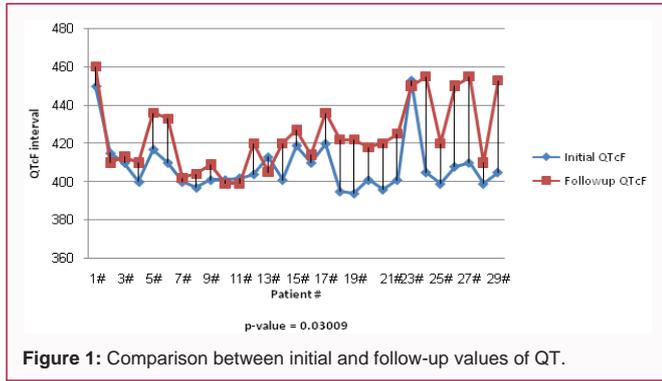
Accepted Date: 08 Oct 2018

Published Date: 15 Oct 2018

Citation:

Kheroo K. Effect of Tyrosine Kinase Inhibitor in Patients with Chronic Myeloid Leukemia (Cytogenetic, Molecular response) in Mosul-Iraq. Am J Leuk Res. 2018; 2(2): 1014.

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factor independence, increased proliferation, genetic instability and suppression of apoptosis in leukemia [1]. Tyrosine kinase inhibitor has revolutionized the treatment of chronic myeloid leukemia and allow a much faster reduction in BCR-ABL1. The response to TKI can be monitored by hematological, cytogenetic and molecular response, patient with cytogenetic and molecular response as early as 3 months has a better outcome and prognosis than non-responder [2]. Patient who are resistant or cannot tolerate the first line TKI imatinib still benefit from the second line drug like nilotinib and dasatinib. Fluorescence in situ hybridization (FISH) is a highly sensitive molecular genetics technique, which enables to detect Breakpoint Cluster Region – Abelson (BCR-ABL) complex and minimal residual disease in all (ph) positive CML patients not only in metaphase but also in interphase cells. This technique enables to detect several nucleic acid target sequences simultaneously with different fluorescent colors [3]. Real-time Quantitative Polymerase Chain Reaction (RQ-PCR) by detecting the presence of BCR-ABL1 mRNA is used to monitor the molecular response to TKI, it is capable of detecting low levels of disease and is >3 logs more sensitive than conventional cytogenetic [4]. In addition, the RQ-PCR can be performed on peripheral blood samples, making it more convenient than bone marrow sampling [5]. Imatinib was available as first line treatment in Iraq and in Mosul since 2002. The FISH analysis was carried on at central authorized laboratory in Baghdad. The Quantitative Reverse Transcriptase Polymerase Chain Reaction (QRTPCR) was carried on at authorized laboratory in Baghdad and Mosul. The aim of this study is to evaluate the cytogenetic, molecular response, effect particularly on bone and heart for imatinib and nilotinib respectively.

Patients and Methods

One hundred seventy six patients with chronic phase Philadelphia positive chronic myeloid leukemia on imatinib are registered in the Mosul hematology center since 2002, eighty seven are eligible for review and follow-up, sixty patients are transferred to continue treatment on their original residence in other governorate (Kirkuk, Salahaldien, Anbar and Diyala) and twenty nine patients on nilotinib as second line treatment treated at Ibn-sena teaching hospital/ outpatient hematology department were reviewed between April 2002-April 2014.

Eligible patients were 18 years or older, mean age 41.17 year (range 18-75 year), 42 males and 45 females all are in chronic phase CML. The 29 patients on nilotinib, of them 16 were males and 13 were females, mean age 43 year (range 25-70 years) initially treated by imatinib and switched to nilotinib due to primary, secondary failure or drug intolerance. Imatinib mesylate 400 mg was given orally daily. Cytogenetic response(FISH): categories; no cytogenetic

Table 1: Demographic characteristic of the patients on Imatinib.

Median age(range), years	41.17(18-75)
Male %	48.27
Female%	51.72
Median CML duration(range) years	8.02(4-12)
Mean imatinib dose intensity(range),mg/d	432.14(300-800)
Median duration of imatinib treatment(range),years	8.02(4-12)

response >95%ph+, minor cytogenetic response 66%-95% ph+, partial cytogenetic response 36%-65% ph+, major cytogenetic response 1% to 35% ph+ and complete cytogenetic response <1% ($\leq 1/200$) positive Interphase nuclei [2]. The FISH analysis was carried on at central authorized laboratory in Baghdad. Four ml of peripheral blood in heparinized tube were used to prepare cells in interphase stage according to standard cytogenetic protocol. Hybridization was done using Dual color-Dual fusion Kit from Applied Metasysteme (Germany). The test was repeated every 3 months and for those with complete cytogenetic response every 6 months. Escalation of imatinib to 600-800mg daily was considered for patients who did not obtain a Complete Hematological Response (CHR) after at least 3 months of therapy [6], those who relapsed after achieving CHR, those who did not achieve a major cytogenetic response (ph-positive interphases less than 35%) after 12 months of therapy, or those with cytogenetic relapse (increase of ph-positive interphases by at least 30%) [7,8] The dose of nilotinib is 400 mg twice daily. The Gene Expert BCR-ABL Monitor Assay is an automated test for quantifying the amount of BCR-ABL transcript as a ratio of BCR-ABL-/ABL1 and linked to an International Scale (IS) and calibrated to WHO standards. The test carried on authorized laboratory initially in Baghdad then in Mosul, (both laboratory using the same standard and sponsored by Novartis) repeated every 3 months and for those with MMR (4.5 Log) every 6 months then every 12 months later on. Definition of Molecular Response: Major Molecular Response (MMR) corresponds to 0.1% BCR-ABLIS, the terms Complete Molecular response 4,4,5,5 (CMR4, CMR4.5 and CMR5) have started to be used to indicate levels of disease that are 0.01% BCR-ABLIS (4-log reduction from IRIS baseline), 0.0032% BCR-ABLIS (4.5-log reduction from IRIS baseline) and 0.001% BCR-ABLIS (5-log reduction from IRIS baseline), respectively [9,10].

To study the effect of imatinib mesylate on bone mineral density fifty out of 87 patients were enrolled for this purpose. Their age ranges 18-50 year with a mean age of 33 year. They are 30 male and 20 female. All the patients are on treatment by imatinib for at least 2 year. For all the patients' ionized calcium, total calcium, serum albumin, serum alkaline phosphatase, serum phosphate, urea, and creatinine

Table 2: Cytogenetic response.

Cytogenetic response	Imatinib 400mg	Imatinib 600-800mg	Total	Nilotinib 800 mg
	No. (%)	No. (%)	No. (%)	No. (%)
CcyR (<1% ph+)	63 (88.7)	11(68.75)	74(85.0)*	13 (44.83)
McyR (1%-35% ph+)	8 (11.3)	4 (25.0)	12(13.8)*	7 (24.14)
Minor (66%-95% ph+)	---	1(6.25)	1 (1.2)	9 (31.03)
Total	71 (100.0)	16 (100.0)	87(100)	29 (100)

* P=0.000 comparing CcyR vs. McyR, (85.0% vs. 13.8%) using Z-test for one proportion.

Table 3: Molecular response to Imatinib.

Molecular response	No.	%
Complete Molecular Response		
Log 4	25	28.74
Log 4.5	7	8.05
Log 5	32	36.78
Major Molecular Response	11	12.64
Loss of response	12	13.79
Total	87	100

Table 4: Molecular response to Nilotinib.

Molecular response	No	%
Complete Molecular Response		
Log 4	4	13.79
Log 4.5	3	10.34
Log 5	3	10.34
Major Molecular Response	10	34.48
No response	9	31.05
Total	29	100

measured at baseline, 6 months and 12 months. Serum levels of intact parathyroid hormone using TOSOH – AIA-360 (Automated Immunoassay Analyzer). DEXA measurements of the lumbar spine (L2-L4 vertebrae), and femoral neck were performed using a DEXA scanner (GE-Lunar Prodigy; GE Lunar Corp., Madison, WI) with encore software version 10.50 (GE Lunar Corp.). The manufacturer's precision errors (coefficient of variation, 1.5, 1.8, 1.5, 1.0, and 0.5% for the lumbar spine, femoral neck, sites, respectively) were used to determine the minimum detectable significant change (coefficient of variation % \pm 2.77) in Bone Mineral Density (BMD) at each site.

Twenty nine patients on nilotinib as second line treatment were followed to evaluate the cardiotoxicity. 16 male and 13 female with a mean age of 43 year (25-70 years) were included for this purpose. Four of these patients had moderate to severe risk factor for cardiovascular disease, which is defined as >10% cardiovascular risk over 10 years based on the Framingham Coronary Heart Disease Risk Score [11]. It was calculated online using the MD calculator [12]. All patients had a base-line standard 12-lead Electrocardiography (ECG) using the MAC 1600 resting ECG system by GE healthcare, with a follow-up ECG's performed every 6 months during the study period. These ECG's were used to assess any occurrence of QT prolongation, ischemic changes, or arrhythmias while the patient is on nilotinib therapy. Assessment of prolongation of the QT interval was based on the long-QT syndrome diagnostic score [13]. The corrected QT interval was calculated using the Fridericia formula (QTcF) [14]. Noninvasive cardiac imaging was performed using the resting transthoracic Echocardiography (Echo) with its 2-dimensional and M-mode views, using the MCMD02AA model of Philips Health care product. All patients had their Echo study at the beginning of their Nilotinib and every 6 months during the study time, performed by the same cardiologist. The aim was to assess left ventricular systolic and diastolic functions, and the occurrence of any pericardial disease.

A significant cardiac event was defined as the occurrence of symptomatic arrhythmia, prolongation of QTcF >60 millisecond from baseline, QTcF >500 millisecond, new left ventricular dysfunction, acute coronary syndrome, significant pericardial effusion, or sudden death.

Statistical Analysis

The standard statistical methods for the analysis of data, to evaluate the effect of imatinib on bone, were used to determine the mean, Standard Deviation (SD), paired t-test, in addition to Pearson correlation and Z-test for one proportion. The statistical results were considered significant at $P \leq 0.05$ by statistical program software known as Med Calc version 12.5.0.0: March 29, 2013.

Results

The median duration of CML is 8 years (range 4-12) and the median duration of treatment by the first generation of the brand tyrosine kinase inhibitor is 8 years (range 4-12), of the 87 patients who were eligible for follow up 74 (85%) achieved complete cytogenetic response, 12 (13.8%) major cytogenetic response and 1 (1.2%-) had minor cytogenetic response (Table 1,2). For those on nilotinib 13 out of 29 (44.8%) have complete cytogenetic response, 7 (24%) major cytogenetic response whereas 9(31%) patients had no response (Table 2). Regarding molecular response 75 patients out of 87 (86.20%) achieved complete and major molecular response whereas 12 (13.8%) patients losses their response to imatinib. For those with complete molecular response 36.78% have 0.001(log 5), 8% 0.0032% (log 4.5) and 28.78% 0.01% (log 4) reduction in BCR-ABL respectively (Table 3). For patients on nilotinib 34.47% has complete molecular response, 34.47% major molecular response, so the overall molecular response is 68.94, whereas 9 patients have no response to the second line TKI (Table 4).

Twelve out of 87 patient died (10 due to CML) and 2 patient died due to event not related to CML (shell injury), so the overall survival rate is 86.20% at 12 year. The 5 years survival rate after nilotinib treatment is 68.94% (20 out of 29).

Decreased serum phosphate levels were observed in 87.88% of patients after imatinib treatment, additionally, total calcium levels were significantly lower during the 6-month time point, or 12 month time point of study, compared with baseline levels whereas ionized calcium were not significantly altered by imatinib treatment (Table 5).

Table 5: Effects of imatinib on serum calcium and phosphate.

Parameter	Normal range(mmol/l)	Baseline	6 months	P_ value	12 months	P_ value
Phosphate	(0.65–1.45)	(0.94 –1.70)	(0.45–1.14)	0.0001	(0.57_1.06)	0.0001
Total calcium	(2.10–2.55)	(2.19 –2.49)	(2.08 –2.39)	0.001	(2.03_2.32)	0.01
Ionized calcium	(1.10–1.25)	(1.13–1.33)	(1.11–1.26)	NS	(1.13_1.25)	NS

Table 6: The effect of imatinib on (L2-L4) BMD.

DEXA study time					
DEXA study results	At started time of study		After 12 months of start study		
	No.	%	No.	%	
Normal (T-score >-1)	35	70	36	72	
Osteopenia (T-score >-2.5 <-1)	15	30	14	28	
Osteoporosis (T-score <-2.5)	0	0	0	0	
Total	50	100	50	100	

There were no detectable effects of imatinib on blood urea or serum creatinine levels), suggesting that imatinib treatment had no deleterious effects on renal function. There is increase in mean PTH during the 12 month time point, but this increase is not significant. DEXA analysis revealed no significant changes in L2–L4 lumbar vertebral BMD but there is significant change at femoral neck (Table 6,7).

For patient on nilotinib, prolongation of QTcF was observed in 80% with a mean of 13.56 milli second. This was statistically significant (p-value =0.03009). However, none of our patients develop a clinically significant prolongation of the QTcF (an increase of >60 millisecond from the baseline, or an absolute duration >500 millisecond) (Figure 1). There was no significant difference in left ventricular ejection fraction % from the baseline (Figure 2). None of the patients develop major cardiac event.

Discussion

The responses to the tyrosine kinase inhibitor in patients with chronic myeloid leukemia in chronic phase are currently monitored by hematological, cytogenetic and molecular test by FISH and PCR-RT [15]. The median duration of CML is 8 years (range 4-12) and the median duration of treatment by the first generation of the brand tyrosine kinase inhibitor is 8 years (range 4-12), although and due to the circumstances in the country i.e. the sanction and Mosul crisis the brand was not always available and the generic form had been used occasionally instead (Imatib from Cipla), of the 87 patients who were eligible for follow up 74 (85%) achieved complete cytogenetic response, 12 (13.8%) major molecular response and 1 (1.2%-) (Table 3)) had minor molecular response and these finding is inconsistent with other studies [16,17], and for those on nilotinb10 out of 29 (44.8%) have complete cytogenetic response, 10 (24%) major cytogenetic response whereas 9 (31%) patients had no response and these finding is in agreement with other study [18]. Regarding molecular response 75 patients out of 87 (86.20%) achieved complete and major molecular response whereas 12 (13.8%) patients losses their response to imatinib. For those with complete molecular response 36.78% have 0.001 (log 5), 8% 0.0032% (log 4.5) and 28.78% 0.01% (log 4) reduction in BCR-ABL respectively.

The result is encouraging taking in consideration the horrible situation in the city which is reflected in the treatment of these patients resulting in interruption of their treatment or to use the generic form of the medicine if it is available, so such factor to be

Table 7: The effect of imatinib on (femoral neck) BMD.

DEXA study time				
DEXA study results	Start time		After 12 months	
	No	%	No	%
Normal (T-score >-1)	19	38	10	20
Osteopenia (T-score >-2.5 <-1)	31	62	39	78
Osteoporosis (T-score <-2.5)	0	0	1	2
Total	50	100	50	100

considered as a cause of failure or lack of response to TKI in addition to the well-known criteria and to have different guideline and follow up for patients from country suffering from such event and have limited resources. Of the 29 patients on nilotinib 10 patients achieved complete molecular response (34.47%), 10 with major molecular response (34.47%) whereas 9 patients had no response (31.06%). The 5 years survival rate after Nilotinib treatment is 68.95% (20 out of 29).

Twelve out of 87 patient died (10 due to CML) and 2 patient died due to event not related to CML (shell injury), so the overall survival rate is 86.20% at 12 year which is lower than previous published data [19].

While CML is not generally associated with a skeletal phenotype, the possibility that the return to normal marrow cellularity or hypo cellularity after imatinib therapy may indirectly affect bone metabolism should be addressed. Because this study could not be placebo-controlled, it cannot be concluded whether the observed effects of imatinib on the skeleton were due to disease remission or were due to direct actions of imatinib on osteoclasts and osteoblasts. However, previous data from CML patients treated with interferon suggest that dysregulated bone remodeling is not a general consequence of disease remission [20]. Consistent with previous studies, imatinib therapy is associated with a decrease in serum phosphate and total calcium (corrected to serum albumin level) and an increase in mean of PTH. The increase in PTH is not significant in comparison with other studies which compare the baseline of PTH at any point of imatinib therapy [21] and the studied group was already on imatinib since two years or more. The normal urea and creatinine observed in the studied group exclude renal osteodystrophy as a cause for the change in calcium and phosphate. There is significant decrease in Bone Mineral Density (BMD) at femoral neck whereas there is no change at the level of lumbar vertebrae which in accordance with

study by O'Sullivan et al. [22]. However, the mechanism responsible for this site-specific bone loss remains to be determined possible explanation may be due to the anatomical and cellular composition of the proximal femur.

Nilotinib as targeted therapy have well-recognized cardiac toxicity [23]. Twenty four out of 29 patients on nilotinib had a QTcF prolongation between 2-28 milliseconds this is in agreement with other study [24]. Our study did not reveal any significant decline in LVEF% observed by Echo study in line with other studies [25]. None of our patients developed any clinical or ECG evidence of ischemic heart disease, whereas 8% of patients in the study by Kim TD et al. [25] develop acute coronary syndrome, but no direct link between these event and nilotinib is approved and as reported by other studies patients with vascular events may have other risk factors i.e. hyperglycemia, increase in cholesterol, so nilotinib may aggravate pre-existing atherosclerotic conditions [26].

Conclusion

The complete cytogenetic response is 85% for those on imatinib and 86.20% have complete and major molecular response. The complete cytogenetic response to nilotinib is 44.8% and 68.95% having complete and major molecular response. The overall survival rate is 86.20% at 12 year of imatinib therapy. The 5 years survival rate after nilotinib treatment is 68.96%. Hypophosphatemia, hypocalcaemia and secondary hyperparathyroidism, develops in patients taking imatinib with no change in BMD of L2-L4 vertebrae. Significant decrease in femoral neck BMD observed after 12 month time point. Nilotinib prolonged the QTcF interval by an average of 13.56 millisecond with no adverse cardiac events.

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