



*Original Research Article*

**Assessment of Responses and Adverse Effect between Chronic Myeloid Leukemia Patients Receiving Imatinib Versus Nilotinib Attending Merjan Teaching Hospital / Hematological Unit**

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**Abstract**

Chronic myeloid leukemia (CML) is a myeloproliferative disorder affecting hemopoietic stem cells and affect predominantly granulocyte progenitor line. Imatinibmesylate is the first molecular targeted therapy for the treatment of CML, the next one is the Nilotinib which is also a selective inhibitor of tyrosine kinase. The aim of this study was to evaluate the hematological, cytogenetic and molecular responses in patients with CML receiving Tyrosine Kinase Inhibitors attending hematological unit of Merjan hospital and to compare between Imatinib and Nilotinib drugs regarding their responses and adverse effects. Complete hematologic response (CHR) were attained in all patients in this study, cytogenetic response to Imatinib achieved in (86.3%), optimal response in (37.8%) and delayed response more than one year (48.4%) . 78.5% of Nilotinib switched patient achieved complete cytogenetic response, (35.7%) optimal response and (42.8 %) got delayed response, (21.4%) of patients showed failure of cytogenetic response. Molecular response achieved in (72.7%) and (53.5%) to Imatinib and Nilotinib switched patients respectively, others (46.5%) of Nilotinib switched patients showed molecular failure. The vast majority of adverse effects were minor for both drugs, liver function tests and amylase enzyme showed minor elevation in a minority of patients. Frequent cytogenetic and molecular monitoring are necessary to define patients with optimal responses and to switch those with suboptimal one to another drug so to achieve optimal responses.

**Key words:** CML, hematological response, cytogenetic response, molecular response, Gleevec, Tasigna.

**تقييم الاستجابة والاعراض الجانبية بين مرضى سرطان كريات الدم البيضاء المزمن لعقاري الایماتینیبوالنیلوتینیب في مستشفى مرجان التعليمي/ وحدة امراض الدم**

**الخلاصة**

سرطان كريات الدم البيضاء المزمن هو مرض ناتج من زيادة نشاط الخلايا المكونة لكريات الدم البيضاء في نخاع العظم نتيجة حدوث طفرة جينية. هناك عقاقير تعمل على إيقاف نشاط هذا المرض وتشمل مثلًا عقار الایماتینیب المتوفر قديمًا ومنها الجديد مثل عقار النیلوتینیب. الهدف من الدراسة هو مقارنة الاستجابة لهذه الادوية وتشمل استجابة الدم والاستجابة على مستوى الكروموسومات والجينات مع مقارنة الاعراض الجانبية ومدى تأثيرها على وظائف الكبد وانزيم اميليز البنكرياس. وجدت هذه الدراسة ان هناك نسبة كبيرة للاستجابة على مستوى الدم للعقارين ونسبة استجابة عالية على المستوى الخلوي لعقار الایماتینیب ولكن منهم نسبة عالية كانت استجابة متأخرة مما كان له الاثر بان تكون هناك نسبة عالية من عدم الاستجابة على المستوى الجيني . اما المرضى الذين حولوا الى العقار الثاني/النیلوتینیب بسبب عدم استجابتهم للعقار الاول فكانت استجابتهم على المستوى الخلوي عالية و اكثر من نصفهم كانت لديهم استجابة على المستوى الجيني. الاعراض الجانبية لكلا العقارين بسيطة وكان هناك ارتفاع بسيط في انزيمات الكبد وانزيم اميليز البنكرياس في نسبة قليلة من المرضى دون الحاجة لايقاف العلاج. ينصح بمتابعة المرضى بصورة مستمرة على المستوى الخلوي والمستوى الجيني لمعرفة استجابة المرضى وتحويلهم الى العلاج الثاني في الوقت المناسب.

**الكلمات المفتاحية:** سرطان كريات الدم البيضاء المزمن, استجابة الدم لعلاج, الاستجابة الخلوية, الاستجابة الجينية, عقار كليفك, عقار تاسيكتا.

## **Introduction**

**C**hronic myeloid leukemia (CML) is a myeloproliferative disorder affecting hemopoietic stem cells and affect predominantly granulocyte progenitor line. It is characterized by acquired chromosomal abnormality which called the Philadelphia chromosome (ph+) in 95% of cases [1], the Philadelphia chromosome is a genuine cytogenetic signature of the disease which is a chimeric protein made from reciprocal and balanced translocation (without loss of genetic material) between the long arms of chromosomes 9 and 22 t(9; 22)(q34;q11) that result in very short chromosome karyotype of 22 chromosome and very long chromosome 9. The mechanism for this result in the fusion of two genes: the ABL gene located in 9q34 and the gene BCR located in 22q11, which generate a hybrid gene called BCR-ABL encoding a chimeric protein 210 KDa (P 210 BCR-ABL) responsible for dysregulated tyrosine kinase which plays a major role in the development of the disease [2].

The molecular basis of this translocation is well known, with its cellular consequences, which allowed on one side a better understanding of the pathophysiology of disease, and on the other side assessment of established tools used for diagnosis and therapeutic monitoring [3,4].

Indeed. The introduction of the inhibitors of tyrosine kinase activity of BCR-ABL (Imatinib and Nilotinib) have changed the therapeutic management of this disease, because this targeted therapy has an anti-tyrosine kinase activity which allowed sustained and durable responses that are expressed at 3 different levels:

1-Hematological response: corresponding to the disappearance of splenomegaly and normalization of hematological parameters.

2-Cytogenetic response: corresponding to the decrease in mitosis of Ph+; it is

measured as a percentage of residual Ph+ cells.

3-Molecular response: corresponding to the decrease in BCR-ABL transcript gene.

Imatinibmesylate is a powerful and selective competitive inhibitor of BCR-ABL tyrosine kinase, it the first molecular target therapy for the treatment of CML [5,6].

The newly prescribed tyrosine kinase inhibitor was Nilotinib (Tasigna)<sup>®</sup> was used in chronic phase and accelerated phase in patients who are no longer benefiting from, or did not tolerate Imatinibmesylate (Gleevec) [7].

## **Materials and Methods**

A cross sectional study conducted at the hematology unit of Marjan hospital, Babylon, Iraq from the early January 2014 to the end of December 2014, 94 patients (42 male, 52 female) were enrolled in this study at their monthly follow up and drug intake.

Information taken about age, sex, residence, duration of the disease, any complications, follow up of their responses, all (hematological, cytogenetic and molecular) responses with measurement of liver function tests and amylase enzyme.

Ninety four total regularly attend patients, 66 patients still on Gleevec treatment while 28 was shifted to Tasigna because of no or failure of molecular response.

The chronic phase was defined according to the criteria recommended by WHO [8].

Response criteria were adapted from the National Comprehensive Cancer Networks (NCCN) clinical practice guidelines [9].

Complete hematological response was defined as a white blood cell count less than  $10 \times 10^9/L$  without immature cells, with less than 5% basophils, and a platelet count less than  $450 \times 10^9/L$  with no organomegaly.

Cytogenetic response was assessed according to FISH analysis and categorized as complete (absence of Ph positive cells),

partial (1%-35% Ph positive cells), minor (36-65% Ph positive cells), minimal (66-95% Ph positive cells), or no response (more than 95% Ph positive cells) [10]. All patients were proved to be Ph positive through fluorescence in situ hybridization (FISH) analysis, or p210 BCR/ABL

transcript positive done via RT-PCR assay of peripheral blood or bone marrow aspirate samples. The 2013 ELN Recommendations support changing to second generation Tyrosine Kinase Inhibitors for patients with treatment failure.

**Table 1:**Optimal and Suboptimal Responses to Tyrosine Kinase Inhibitors

Optimal Responses	Suboptimal Response
3 mon: Ph + ≤ 35% and/or BCR-ABL ≤ 10%	3 mon : No Cytogenetic response
6 mon : Ph + 0 % and/or BCR-ABL < 1%	6 mon: < Partial Cytogenetic response
12 mon : BCR-ABL ≤ 0.1 % (MMR)	12 mon: Partial Cytogenetic response
At any time : BCR-ABL ≤ 0.1 % (MMR) (MMR : Major molecular response)	18 months: < Major molecular response
	At any time: Loss of CCYR, Clonal chromosomal abnormality, confirmed loss of MMR, or new mutation [11].

Per ELN recommendation, BCR-ABL more than 10% at 6 months is considered treatment failure and the patient should receive another treatment[12].

**Results**

The base line characteristics of the 94 patients enrolled in this study were 42 male and 52 female with male to female ratio (1:1.2). The mean age was 44.7 (ranging from 8 to 85 years), the majority of patients were from Babylon city (64.6%), 28.7% from Al-diwania city, 4.3 % from Al- cimawa, 1.1% from karbala. The mean duration of Imatinib treatment was(4.5) years (ranging from 1 year to 15 years), while the mean duration of Nilotinibwas 2.5 years( ranging from 1-3 years).

Complete hematological response was achieved in all patients in this study including both in Imatinib and Nilotinib drugs.

Cytogenetic response showed that from 66 patients on Imatinib 57 (86.3%) achieved complete cytogenetic response, 25 patients (37.8%) achieve complete cytogeneticresponse during the ideal time, while 32 patients (48.4%) have delayed complete cytogenetic response more than one year (table 2).

About molecular response 48 patients out of 66 (72.7%) achieved molecular response while 18 patients (27.2%) still had molecular failure (table 3).

Regarding Nilotinib, 28 patients studied , they were switched to the drug because of loss or failure of molecular responseor because the patient developed accelerated phase while on Imatinib treatment, 22 patients (78.5%) achievedcomplete cytogenetic response, 10 (35.7%) of them were achieved in the optimal time while the others 12 (42.8%) got delayed complete cytogenetic response (table 2).

Molecular response showed that 15 (53.5%) achieved major molecular response

and other 13 (46.5 %) still have failure of Nilotinib treatment (table 3).  
molecular response despite of 1-3 years of

**Table 2:** Complete Cytogenetic Response Rates to Imatinib and Nilotinib

Drug	Complete Cytogenetic Response ( Ccyto. R.)			Total
	Optimal Ccyto. R.	Delayed Ccyto. R.	Failure	
Imatinib	25 (37.8%)	32 (48.8%)	9 (13.6%)	66
Nilotinib	10 (35.7%)	12 (42.8%)	6 (21.4%)	28
Total	35	44	15	94

**Table 3:** Molecular Response Rates to Imatiniband Nilotinib

Drug	Molecular Response		Total
	MMR	Failure	
Imatinib	48 (72.7%)	18 (27.3%)	66
Nilotinib	15 (53.5 %)	13 (46.5%)	28
Total	63	31	94

**Table 4:** Associations between molecular and cytogenetic Responses Rates

		Molecular Response		Total
		MMR	NO MMR	
Cytogenetic	Optimal R.	28 (90.4%)	3 (9.6%)	31
	Failure	0	21 (100%)	21
	Delayed R.	34 (80.9%)	8 (19.1%)	42
Total		62	32	94

Overall 31 patients both on Imatinib and Nilotinib drugs achieved optimal complete cytogenetic response, 28 (90.4%) got major molecular response while 3 (9.6%) were not. 34 (80.9%) patients out of 42 with delayed complete cytogenetic response achieved major molecular response and 8 (19.1%) showed molecular failure (table 4).

The majority of the 66 patients on Imatinib (63 patients) (95.4%) experience mild

adverse effect such as edema, nausea, muscle cramps, mild bone pain and myalgia, 3 patients only (4.5%) developed severe adverse effect that necessitated temporary discontinuation of the drug such as severe thrombocytopenia, pancytopenia. Patients on Nilotinib showed mild adverse effects only, interestingly 15 patients (22.7%) and 10 patients (35.7%) had no reported side effect on Imatinib and Nilotinib respectively (table 5).

Table (5) shows the main adverse effects of the two drugs in the present study.

**Table 5:** Rates of Imatinib and Nilotinib adverse effects.

<b>Imatinib Adverse effects n(%)</b>	<b>Nilotinib Adverse effects n(%)</b>
Lassitude 12(18)	Headache 10 (35.7)
Odema20 ( 30.3)	Joint pain7 (25)
Bone and Joint pain 15 (22.7)	Nausea 5 (17.8)
Vomiting 3 (4.5)	Fever 3 (10.7)
Skin rash3 (4.5)	Jaundice 2 (7)
Fever 5 (7.5)	Itching 3 ( 10.7)
Loss of hair 1 (1.5)	Skin rash 2 ( 7)
Abdominal pain 2 (3)	Menorrhagia 2 ( 7 )
No Side effect15 (22.7)	Frequency of Urination 1 ( 3.5)
Sever complications 3 (4.5)	No Side effect 10 (35.7)

Measurements of liver function tests for patients on Imatinib showed that only 3 patients out of 66 patients (4.5%) had abnormal liver function tests which is minor elevation (< 3 times normal) that not necessitate discontinuation of the drug

while 6 patients on Nilotinib out of 28 patients (21.4%) also develop minor elevation of liver function tests which does not require dose adjustment of the drug (table 6).

**Table 6:** Liver Function Tests in Imatinib versus Nilotinib

	<b>drugs</b>		<b>Total</b>
	<b>Imatinib</b>	<b>Nilotinib</b>	
LFT Normal	63	22	85
Abnormal	3 (4.5%)	6 (21.4%)	9
Total	66	28	94

Serum amylase enzyme measurement showed that 3 patients (4.5 %) out of 66 patients on Imatinib showed a minor

elevation, while 2 patients out of 28 on Nilotinib (7.1%) showed a twice of normal level of amylase enzyme ( table 7).

**Table 7:** Amylase Enzyme in Imatinib versus Nilotinib

	<b>amylase</b>		<b>Total</b>
	<b>Normal</b>	<b>Elevated</b>	
Drug Imatinib	63	3 (4.5%)	66
Nilotinib	26	2 (7.1%)	28
Total	89	5	94

**Discussion**

The current available first line treatments for CML are targeted therapy (Tyrosine kinase BCR-ABL inhibitors) imatinib

(Gleevec®) and then nilotinib (Tasigna®). The choice of one of these targeted treatment depends on many factors, the most important being the deeper molecular

response, treatment - free survival and of course financial costs[13].

In the present study, 66 CML patients received 400 mg daily of Imatinib were followed for their, hematological, cytogenetic and molecular responses from the time of diagnosis, all showed hematological response during the study period, (86.3%) achieved complete cytogenetic response, (37.8%) were optimal response and (48.4%) had delayed response (suboptimal) more than one year. (13.6%) showed no response, likewise, Rajappa et al had shown complete cytogenetic response had been achieved in 56%, partial response in 23%, minor response in 17% and no response in 4% patients after a median follow up of 29.5 months[14].

When the results of this study compared to that of IRIS study; at phase 3 IRIS study with median follow up of 12 months, the estimated rates of complete hematological response (CHR) for patients treated with imatinib were 90.48%, complete cytogenetic response (92.9%) which are similar to the result of current study[15]. Of 28 Nilotinib switched patients (78.5%) achieved complete cytogenetic response, more than the rate of responses in phase 3b, open-label, multicenter ENACT (Expanding Nilotinib Access in Clinical Trials) study which showed (50%) of patients developed complete cytogenetic response[16].

Major molecular response (MMR) was achieved in (72.7%) of Imatinib treated patients and (27.2%) showed molecular failure, while Nilotinib switched patients, because of prior molecular failure, achieved major molecular response in (53.5%) and molecular failure in other (46.5%), in contrary to the preliminary results of the exploratory, United states-based, multicenter, open label study of nilotinib 300 mg twice daily in patients with suboptimal molecular response to imatinib, which demonstrated that (80%) achieved major molecular response within 9 months[17].

Nilotinib is 20- to 50- fold more potent than imatinib against BCR-ABL in vitro, like imatinib, it binds only to the inactive

conformation of the enzyme, preventing it from adopting the catalytically active site [18,19]. Across several phase 2 studies[20-23] Nilotinib has shown efficacy in patients with CML after imatinib resistance or intolerance[24,25] and has subsequently been approved for treating patients with CP-CML or accelerated phase CML who have imatinib resistance or intolerance [26]. In this study imatinib was well tolerated, and the most common adverse effects were edema (30.3%), bone and joint pain (22.7%), lassitude (18%) and (4.5%) of patients developed severe hematological side effects such as pancytopenia and severe thrombocytopenia. These are comparable to that of Kantarjian et al who showed that only 2% of patients discontinued the treatment because of drug-related adverse effects[27].

Nilotinib is also well tolerated in this study and the majority of patients shows only minor adverse effects as headache (35.7%), joint pain (25%), nausea (17.8%), itching and fever (10.7%), jaundice, skin rash, menorrhagia (7%), and no major adverse effect till the end of this study, and these results were comparable to the Katarjian et al study [28].

Liver function tests and amylase enzyme, liver function tests showed minor elevation in (4.5%) of Imatinib treated patients and (21.4%) of Nilotinib switched patients, amylase also showed a minor elevation in (4.5%) patients on Imatinib and twice level of normal in (7.1%) in Nilotinib switched patients, and this result is agreed with the study of Timothy P. Hughes et al study which showed elevated liver functions tests and amylase in 5% and 9.9% of Nilotinib switched patients respectively, and normal liver function tests with (1%) of elevated amylase in Imatinib treated patients [29].

The mildly elevated percentage of abnormal liver function tests and amylase enzyme in Nilotinib switched patients is not surprising as it was associated with introduction of a new drug after failure or intolerance of the first one [30].

**Conclusion**

Treatment of CML patients with first line TKI Imatinib (Gleevec) was associated with optimal hematological and cytogenetic responses in a good percentage of patients. Delayed complete cytogenetic response (suboptimal) occurred in higher percentage than optimal cytogenetic response in Imatinib treated patients, the former showed more than 19% molecular failure as compared with the latter which showed less than 10% molecular failure. The majority of Nilotinib switched patients after Imatinib failure achieved complete cytogenetic response although some showed delayed response and more than half of patients got major molecular response. Both drugs were safe and well tolerated with minor adverse effects.

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