

# Treatment Outcomes of Nilotinib as Second Line Therapy for Chronic Myeloid Leukemia Patients in Karbala Province of Iraq

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**Background:** Second line treatment of chronic myeloid leukemia (CML) is crucial after imatinib therapy failure. In Iraq, nilotinib is the only available second line tyrosine kinase inhibitors (TKIs), making management of CML patients with failure response to 1st generation TKIs as a great challenge to the health system.

**Objectives:** Our study tries to evaluate nilotinib safety and efficacy among CML patients in Karbala province of Iraq as the only drug available as second line treatment for CML patients post imatinib failure.

**Materials & Methods:** This research was carried out in Al-Hussein cancer center in Karbala province of Iraq between January 2012 & December 2020. Nilotinib was used as a second-line treatment for 30 CML patients and their response were assessed by the level of BCR-ABL1 transcription in peripheral blood at 3 months, 6 months and 12 months from starting treatments.

**Results:** The median age was 42.5 years, included 16 males and 14 females with male to female ratio 1.14. According to Sokal score 15 patients were high risk, 11 patients were intermediate risk and 4 patients were low risk. More than 66% of our patients achieved major molecular response (MMR) after starting nilotinib as second line. The BCR- ABL transcription level had a significant reduction from baseline at 3 months, 6 months and 12 months respectively (P value <0.05). Male patients and those who received imatinib for  $\geq 24$  months were better survival.

**Conclusion:** Nilotinib is effective and safe drugs as second line treatment among Iraqi patients.

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## Introduction

Chronic myeloid leukemia (CML) is a hematopoietic disease that is characterized by bone marrow stem cells malignant expansion. It is characterized by t (9;22) (q34; q11.2) translocation which is known as Philadelphia (Ph) chromosome. This translocation leads to BCR/ABL1 gene that encodes an oncogene (P210, more rarely P230 or P190) which produces an abnormal tyrosine kinase activity that causes aberrant myelopoiesis [1].

The development of tyrosine kinase inhibitors (TKIs) has revolutionized CML treatment, resulting in significant improvements in prognosis, response rate, overall survival, and patient outcomes as compared to earlier therapeutic regimens [2].

Many prognostic scoring models for CML risk stratification have been developed throughout the years. Using clinical factors, the Sokal score was used to risk stratify patients at the time of presentation. This classification divides patients into three groups: low risk, intermediate risk and

high risk [3].

Patients with an intermediate or high-risk score had a higher possibility of disease progression, therefore NCCN guidelines, recommend second generation TKIs for high- risk group to decrease the risk of disease progression [4]. Nilotinib is an orally bioavailable drug that is more effective and selective against BCR-ABL than first- generation TKIs (imatinib). It was first licensed in 2007 in the United States and other countries for patients with chronic or accelerated CML who had developed resistance to or were unable to tolerate imatinib [5]. Because of limited resources in our war-torn country all patients offered imatinib as frontline regardless score while second generation TKIs reserved to refractory patients [6].

In this study we trying to assessed the efficacy & safety of nilotinib as the only available second line treatment in CML patients after imatinib failure in Karbala province of Iraq.

## **Materials and Methods**

### **Study design and participants**

This study was conducted at Al-Hussein cancer center in Karbala, on 30 CML patients diagnosed between January 2012 and December 2020. Eligibility criteria for inclusion of patients were as follows: Patients ages  $\geq 18$  years old, good performance status and without any comorbidities with normal hepatic, renal, and cardiac functions. Resistance was defined as no complete hematological response (CHR) at or after 3 months; no minimal cytogenetic response by 6 months; no major cytogenetic response (MCyR) by 12 months; loss of CHR; loss of minor cytogenetic response; loss of MCyR or complete cytogenetic response (CCyR); or the development of clonal evolution. Imatinib intolerance was defined as discontinuation due to a Grade 3/4 imatinib- related adverse effects. Nilotinib was given to patients in doses of 400 mg twice daily and they were followed up for survival.

Follow up after initiating treatment was by complete blood count, blood smear, renal function tests, liver function tests, ECG, and reverse transcriptase polymerase chain reaction (RT-PCR) to establish the response according to BCR-ABL1 transcripts level which defined by the internal scale. No mutational screening was done before establishing of nilotinib therapy for failure responders CML patients, because of its unavailability.

All nilotinib adverse events was registered according to the severity that can be classified by the National Cancer Institute's grading scale [7].

### **Definitions of endpoints**

The primary objective of the research was to assess the MMRs incidence in patients who were intolerance or resistant to imatinib and using nilotinib as second line. The molecular status was evaluated at 3, 6, and 12 months in the first year and in the following years, every 3-6 months.

The secondary objectives were to calculate the overall survival (OS), which was calculated from the time that nilotinib was started till death from any reason, as well as to determine the safety profile of nilotinib. Duration of response was defined as the period of time between the onset of the response and the date when nilotinib is stopped due to progression or death.

Calculation of Sokal score was done by calculation of the proportion of peripheral blood blast cells, the number of platelets, the size of the spleen (measured in centimeters below the costal margin) and the patient's age. The patients were classified into three risk categories according to their individual numerical value: low ( $<0.8$ ), intermediate ( $0.8-1.2$ ), and high ( $> 1.2$ ) [8].

## Ethical considerations

This research was guided by the Helsinki Declaration, and all patients signed a written informed consent form in accordance with the institution’s policies. Ethical approval was obtained from the ethics committee of Karbala teaching hospital in Karbala, Iraq.

## Statistical analysis

All time-to-event analyses were performed with the use of Kaplan-Meier methods and presented by Kaplan-Meier curves SPSS 20.0.0 (Chicago, IL) Minitab 17.1.0 software packages were used for statistical analysis and a  $P < 0.05$  was considered indicative of statistically significant difference.

## Results

There were 30 CML patients on nilotinib as second line treatment enrolled in our study, the median age of our patients was 42.5 years, ranged (18-65) years, with a male: female ratio 1.14. The Median duration of imatinib treatment was 22 months. Median duration of nilotinib was 62.9 months. Half of patients were high risk in 15 patients (50 %), intermediate risk in 11 patients (36.67%) and low risk in 4 patients (13.33%).

The causes of starting nilotinib were primary failure to imatinib in 5 patients (16.67%), secondary failure in 24 patients (80%) and intolerance in 1 patient (3.33%).

Imatinib doses were 800 mg in 22 patients (73.34%), 600 mg in 4 patients (13.33%), 400 mg in 3 patients (10%) and 300 mg in 1 patient (3.33%). Seventeen patients (56.67%) received imatinib for less than 24 months, while 13 patients (43.33%) for  $\geq 24$  months.

Twenty patients (66.67 %) achieved MMR while 10 patients (33.33%) not achieved MMR, the median time to achieve MMR was 9 months. At the end of follow up, one patient (3.33%) had blast transformation and died (Table 1).

Variables	Values (%)
Median age (year)	42.5
Median duration on imatinib therapy (months)	22
Median duration on nilotinib therapy (months)	62.9
Sex, n (%)	
Male	16 (53.33)
Female	14 (46.67)
Sokal score on diagnosis, n (%)	
Low risk	4 (13.33)
Intermediate risk	11 (36.67)
High risk	15 (50.00)
Cause of shifting to nilotinib, n (%)	
Primary failure	5 (16.67)
Secondary failure	24 (80.00)
Intolerance	1 (3.33)
Imatinib dose, n (%)	
300 mg	1 (3.33)
400 mg	3 (10.00)
600 mg	4 (13.33)
800 mg	22 (73.34)
Duration on imatinib, n (%)	

< 24 months	17 (56.67)
≥ 24 months	13 (43.33)
MMR, n (%)	20 (66.67)
No MMR, n (%)	10 (33.33)
Median time to achieve MMR (months)	9
Blast transformation during nilotinib treatment, n (%)	1 (3.33)
Death, n (%)	1 (3.33)

**Table 1. Patients’ Characteristics.**

MMR, Major molecular response

The BCR- ABL transcript level had a significant reduction from baseline at 3 months (P value 0.001), 3 months to 6 months (P value 0.016) and 6 months to 12 months (P value 0.019) (Figure 1).

**Figure 1. Change in BCR-ABL Transcript Level During Nilotinib Therapy.**

There was no significant association between sex, Sokal score, primary failure, secondary failure, intolerance and achieving MMR, P value > 0.05 for each (Table 2).

Variables	MMR (20) (%)	No MMR (10) (%)	P value
Age (years)	42.1 ± 12.09	47.4 ± 13.31	0.298
Sex (%)			
Female	8 (57.14)	6 (42.86)	0.3
Male	12(75.00)	4 (25.00)	
Sokal score (%)			
Low risk	4 (100.00)	0 (0.00)	
Intermediate risk	9 (81.82)	2 (18.18)	0.132
High risk	7 (46.67)	8 (53.33)	
Duration of disease before starting nilotinib (months)	31.55± 27.63	31.7 ± 29.99	0.989
Causes of shifting to nilotinib (%)			
Primary failure	3 (60.00)	2 (40.00)	
Secondary failure	16 (66.67)	8 (33.33)	0.811
Intolerance	1 (100.00)	0 (0.00)	

**Table 2. Comparison between Various Variables According to Achievement of MMR During Treatment with Nilotinib.**

MMR, Major molecular response

The estimated mean OS using Kaplan Meier survival formula was 94.5 months, males were better survival than females (100.06 versus 88.14 months, respectively), the hazard ratio of 1.15 (95% CI: 0.0126 - 104.71). Interestingly, patients who received imatinib for ≥ 24 months were better survival than those who received treatment < 24 months (135.07 versus 63.47 months, respectively), the hazard ratio of 2.349, (95% CI: 0.025 - 213.79). Patients who achieved MMR were higher overall survival (Figure 2 and 3) but this was not statistically significant (Table 3).

**Figure 2. Overall Survival of all Patients.**

**Figure 3. Overall Survival According MMR.**

	Mean±SEM	95% CI of Mean	HR	95% CI	P value
Overall	94.5 ±8.440	78 - 111	-	-	-
Sokal score					
Low	89.66 ±12.461	63.3 - 114	1.074	0.012 - 97.7	0.108
Intermediate	108.636 ±14.808	79.6 - 138			
High	73.75 ± 9.04	56 - 91.5			
Sex			1.15	0.0126 - 104.71	0.011 *
Female	88.142 ±11.947	64.7 - 112			
Male	100.06 ±12.066	76.4 - 124			
Duration imatinib					
<24	63.470 ± 5.471	52.8 - 74.2	2.349	0.025 - 213.79	0.001 *
≥24	135.076 ±10.149	115 - 155			
Causes of shifting					
Primary failure	81.6 ± 11.156	59.7 - 104	1	0.010 - 91.201	0.46
Secondary failure	100.125 ± 9.792	80.9 ± 119			
Age at diagnosis					
<40	99.545 ± 16.275	67.6 - 131	1.025	0.011 - 93.32	0.657
≥40	91.578 ± 9.734	72.5 - 111			
MMR					
MMR	95.95 ± 9.511	77.3 - 115	1.125	0.0141 - 102.56	0.812
No MMR	91.6 ± 17.474	57.4 - 126			

**Table 3. Overall Survival of Chronic Myeloid Leukemia Patients Measured Using Kaplan-Meier Method.**

\* Means significant differences (P ≤ 0.05). HR, Hazard ratio; CI, Confidence interval; SEM, Standard error of the mean; MMR, Major molecular response.

Anemia was the most frequent hematological side effect in 3 patients (10%) followed by thrombocytopenia and leucopenia in 2 patients (6.67%) each. Regarding non hematological side effects, skin rash was the most common side effect in 4 patients (13.33 %) followed by join pain in 3 patients (10.00 %) and edema in 2 patients (6.67%), other side effects are explained in (Table 4).

Hematological side effects	N (%)
Anemia	3 (10.00)
Thrombocytopenia	2 (6.67)
Leucopenia	2 (6.67)
Non-Hematologic side effects	
Skin rash	4 (13.33)
Join pain	3 (10.00)
Edema	2 (6.67)
Palpitation	1 (33.33)
Headache	1 (33.33)
Hair loss	1 (33.33)
Jaundice	1 (33.33)

**Table 4. Nilotinib Side Effects.**

## Discussion

In Karbala province of Iraq, leukemia accounts for more than 6% of cancer patients, whereas CML accounts for more than 24% of leukemia cases [9].

Actually, imatinib become the treatment of choice for newly diagnosed chronic phase CML patients. Despite this, a third of patients will have a poor response to imatinib, either due to primary failure or because they progressed after an initial response [10]. Several mechanisms can cause treatment resistance, such as point mutations in the BCR-ABL kinase domain, leading to poor response and inferior outcomes [11].

Imatinib dose escalation to a daily dose of 600 mg or 800 mg has shown to be effective in patients who have a poor response or disease progression [12]. In our center more than 86% of patients who had progressed disease received the escalating dose before shifting to second line TKIs.

In our study nilotinib therapy was given regardless of mutational analysis because of its unavailability as a screening test for the suboptimal response to or failure of imatinib treatment. Here 66.67% of our patients achieved MMR, which is higher than results in Latin America & Asia where MMR was 58%, 57% respectively [11,13]. The level of BCR-ABL transcription was significantly lower at 3 months, 6 months and 12 months respectively, same results by Yeung et al. where MMR deepen with time [14].

The median age in our patients was 42.5 years which close to previous studies in Karbala governorate but it is decade younger than in western countries, this may be explained by that only (3.4%) of the Iraqi population are above 65 years [6,15,16].

Sokal score is known as predictor to achieve MMR in CML patients [17,18], while in our study there was no correlation between achieving MMR and Sokal score. On the other hand, achieving MMR is a significant predictor for OS [14], but we couldn't find any association between achieving MMR and OS. This is may be due to short follow up time and small sample.

Interestingly, males were better survival than females which is comparable to previous results in Africa although in Europe, females were better survival [18,19]. Meanwhile, patients who had long duration of response to imatinib were better outcomes this was compatible with previous studies in Asia [13].

Drugs side effects had poor impact on leukemia patients' compliance, understanding these side effects and treat them urgently leading to improve outcomes [20]. In our study skin rash was the most common side effect, which is consistent with previous studies [13].

In conclusion, nilotinib is an effective & tolerable second line treatment for Iraqi CML patients regardless of mutational analysis. More than 66% of our patients achieved MMR. Future researches with a greater number of patients in various parts of Iraq are recommended to improve treatment outcomes for CML patients in our country.

### *Authorship*

All the authors contributed equally to this paper.

### *Consent for publication*

All authors have checked this manuscript and declared their consent for publication.

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