DOI:10.31557/APJCB.2024.9.2.137

RESEARCH ARTICLE

A Real World Analysis of Safety and Efficacy of Nilotinib when Used as First Line and Beyond: Retrospective Single Centre Study Representing Largest Cohort of Indian Patients Treated with Nilotinib

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Abstract

Background: Efficacy and toxicity of TKIs may vary depending on the ethnic background or genetic factors; hence it is important to gather data from individual populations pertaining to each drug. The pivotal registration trial had not enrolled any patient from India and there are very limited published studies on its efficacy as well as safety from Indian patients with CML. **Methods:** Hospital Electronic Medical Record was screened for adult (age > 18 years) CML patients registered (n = 1290) at our hospital from 1st May 2018 to 31st December 2022. CML-CP or CML-AP patients, those who have received Nilotinib as 1st line (n = 40) or 2nd line (n = 66) or 3rd line TKI (n = 20) for at least 90 days (3 months) and have at least one RQ PCR BCR: ABL value post Nilotinib initiation, were enrolled in this study (n = 126). **Results:** Eighty (74.1%) patients achieved BCR/ABL of ≤1% at 12 months. MMR and MR4 at 12 months was seen in 44 (40.7%) and 19 (17.6%) patients respectively. The most common haematological toxicity was thrombocytopenia of any grade seen in 54 (42.8%) patients. **Conclusion:** Our study demonstrates that treatment with Nilotinib was well-tolerated in Indian patients and was effective in achieving molecular remission rates in 1st, 2nd or 3rd line therapy in the real-world setting. Safety and efficacy were in line with published western or Asian studies.

Keywords: Chronic Myeloid Leukemia- Nilotinib- Indian Patients- Tyrosine Kinase Inhibitor

Asian Pac J Cancer Biol, **9 (2)**, 137-147 Submission Date: 01/08/2024 Acceptance Date: 03/23/2024

Introduction

Chronic myeloid leukemia (CML) is a clonal disease of the hematopoietic stem cells associated with a specific chromosomal translocation [t(9;22)] which leads to constitutive expression of the BCR-ABL1 kinase resulting in the manifestation of CML [1, 2]. With development of Imatinib in early 2000s, there was a paradigm shift in management of CML and imatinib became standard of care for patients with CML, especially in the chronic phase [3]. Pivotal International Randomized Study of Interferon and STI571 (IRIS) trial demonstrated the long term safety and efficacy of imatinib with an estimated overall survival (OS) rate of over 80% after 8 years of treatment and 83.3% after 10 years of treatment [4-6]. Imatinib resistance is not uncommon and approximately 20–30% of patients develop resistance or intolerance to imatinib leading to its discontinuation [7].

Currently four BCR-ABL1 tyrosine kinase inhibitors (TKIs) are approved for frontline therapy: imatinib, dasatinib, bosutinib and Nilotinib. Use of any of these

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TKIs in CML patients produce near-normal quality of life and life expectancy if treatment compliance is ensured, optimal efficacy monitoring is done, side effects are managed in evidenced based manner and prompt therapy change is done at the earliest sign of true treatment resistance [6, 8-12].

Nilotinib, a second generation oral TKI, was initially developed and approved to treat patients with CML who are resistant or intolerant to imatinib [13]. Nilotinib was approved in 2007 for the treatment of imatinib resistant CML-CP or for patients with CML in the accelerated phase (CML-AP) based on the results from the pivotal registration trial CAMN107A2101 [14, 15]. Subsequently, in 2010, based on results from pivotal phase III ENESTnd study, it was approved for the treatment of newly diagnosed patients with CML-CP or CML-AP [16].

Efficacy and toxicity of TKIs may vary depending on the ethnic background or genetic factors; hence it is important to gather data from individual populations pertaining to each drug. The pivotal registration trial had not enrolled any patient from India. Nilotinib has been available in India since 2010, however there are very limited published studies on its efficacy and safety in Indian patients with CML [17,18]. Through this retrospective real world analysis, we aim to present efficacy and safety profile in real world use of Nilotinib as first line and later lines of therapy in routine daily practice.

Materials and Methods

General Study details

This was a retrospective observational study done in the Medical Oncology department of a tertiary care cancer centre in India. Approval to conduct this study was obtained from the Institute Ethics Committee. Waiver of consent was obtained from IEC in view of the retrospective nature of this study. No funding was taken for the study.

Participants

We enrolled adult (age > 18 years) patients (n = 126) with chronic myeloid leukemia (CML-CP or CML-AP) patients under our follow up and has received Nilotinib as 1st line (n = 40) or 2nd line (n = 66) or 3rd line TKI (n = 20) for at least 90 days (3 months). It was essential to have at least one RQ PCR BCR: ABL value post Nilotinib initiation to enroll patients in this study.

Aims and Objective

To determine efficacy of Nilotinib in different lines in terms of achievement of Early Molecular Response (EMR) and Major Molecular response (MMR). To derive adverse effect profile in terms of haematological (anemia, thrombocytopenia, neutropenia) and non-haematological toxicity.

Study Methodology

Hospital Electronic Medical Record was screened for adult (age > 18 years) CML patients registered (n = 1290) at our hospital from 1st May 2018 to 31st December 2022. Cutoff date for data analysis was 31st Aug 2023. This list was screened for all patients who were diagnosed as CML-CP or CML-AP and prescribed Nilotinib in any line of therapy (n = 148). Among these patients, those who have received Nilotinib as 1st line (n = 40) or 2nd line (n = 66) or 3rd line TKI (n = 20) for at least 90 days (3 months) and have at least one RQ PCR BCR: ABL value post Nilotinib initiation, were enrolled in this study (n = 126).

Electronic Medical Record clinical notes and Laboratory records were used to collect safety and clinical response data. As institute policy we do safety assessments, including haematological and biochemical laboratory investigations at baseline, every month for the first 3 months, and every 3 months thereafter. This data was derived from Electronic Medical Record. Additional Clinical Data (eg previously done ECGs, non haematological adverse effects) were collected through case record form when these patients visited OPDs in the time period of 1st Jan 2023 to 31st may 2023. Complete blood and differential cell counts were used to assess the hematologic response. Complete hematologic response (CHR) was defined as platelet count $<450 \times 10^9$/L, white blood cell (WBC) count $<10 \times 10^9$/L, without immature granulocytes, and with <5% of basophils, and non palpable spleen. We as institute policy perform cytogenetic study only at baseline and do not perform cytogenetic response assessment in CML patients at follow up. Molecular response assessments were conducted at in house laboratory using quantitative real-time reverse transcriptase polymerase chain reaction (RQ-PCR) to quantify the BCR-ABL1 transcripts using peripheral blood samples.

Statistics

The study did not have a formal sample size calculation, as this was a non interventional, observational study. Continuous variables were summarized by mean, median, standard deviation (SD), minimum, maximum and 95% confidence intervals (CIs), and the categorical variables were summarized by counts and percentages in the frequency table. The time-related variables were analysed using the Kaplan–Meier (KM) method.

Results

A total of 148 patients were prescribed and started on Nilotinib in any line of therapy. Thirteen patients discontinued within 3 months of therapy due to financial reasons and were shifted to imatinib (n = 10) or dasatinib (n = 3). Six patients were lost to follow up after initiation and 4 patients discontinued Nilotinib (within 3 months) due to adverse effect as severe myalgia (n = 1), thrombocytopenia (n = 2) and development of new onset psoriasis (n = 1). All 4 patients were shifted to imatinib. A total of 126 patients met eligibility criteria and hence were included in study. Among enrolled patients, 40 patients received Nilotinib as 1st line TKI, 66 received Nilotinib as 2nd line TKI and 20 patients received Nilotinib as 3rd line TKI.

Table 1. Shows Characteristics of Patients who Were Started on 1st Line Nilotinib (n = 40)

Characteristics	N (%)	Median (Range)
Age, Median (range)		32 (21-68)
>40 years	6 (15)	
<40 years	34 (85)	
Sex		
· Male	24 (60)	
· Female	16 (40)	
Disease Phase		
· Chronic Phase	32 (80)	
· Accelerated Phase	8 (20)	
Baseline Laboratory values		
· Hb gm/dL, median (range)		10.4 (5.9-14.8)
· White blood cells (× 10^9/L), median (range)		128.7 (5.4-424.4)
· Platelet count (× 10^9/L), median (range)		325 (35-1811)
· Peripheral blood blasts (%), median (range)		3 (1-17)
· Bone marrow blasts(%), median (range)		4 (1-18)
· Basophils (%), median (range)		9 (3-21)
Spleen (bcm), median (range)		6 (0-18)
EUTOS Risk Score, median (range)		92.5 (28-170)
EUTOS Risk group		
· High Risk	23 (57.5)	
· Low Risk	17 (42.5)	

EUTOS, European Treatment and Outcomes Study (EUTOS) score

Nilotinib as first line therapy in CML

Forty patients received Nilotinib as first line TKI and the median age of the study population was 32 years (range, 21–68 years), of whom 24 (60%) were male. Thirty two (80%) of the patients were in CML-CP and 8 (20%) in CML-AP at diagnosis as described in Table 1.

Median duration of follow up of these patients was 17 months (range 7-79 months). The cumulative EMR and MMR rates by 3 months were 82.5% and 10%, and none of the patients had achieved MR4 (Table 2). Among 7 patients who didn't achieve EMR at 3 months, 1 progressed to blast crisis at 4 months, two patients discontinued Nilotinib at 7 months due to intolerance (persistence grade 3-4 thrombocytopenia) whereas 4 patients were continued on Nilotinib and all of these patients achieved optimal response at 6 months (BCR-ABL1 ≤ 1%) and hence were continued on Nilotinib thereafter. On patient who achieved EMR at 3 months progressed with BCR/ABL of more than 10% at 12 months and hence was switched to dasatinib at 13 months.

Thirty three patients were eligible for analysis at 12 months (Three patients discontinued Nilotinib before 12 months and 4 patients had follow up of less than 12 months). Of these 33 patients, 14 (42.4%) achieved MMR at 12 months and half of these patients [7 patients, 21.2%] had also achieved MR4 at this time point. As per ELN 2020 guidelines [19], five patients were classified as failure at 12 months (BCR-ABL1> 1%). Of these 5 patients, Nilotinib was switched to dasatinib in one patient and rest four were continued on Nilotinib on physicians discretion as BCR/ABL levels in these patients were in the range of 1-3%. Three of these patients achieved BCR-ABL1 ≤ 1% at 18 months follow up and one patient is yet to reach 18 months follow up.

Out of forty patients, 4 (10%) discontinued Nilotinib. Reason for Nilotinib discontinuation was intolerance (persistent grade 3/4 thrombocytopenia) in 2 patients and failure in 2 patients including one patient who progressed to blast crisis.

The most common haematological toxicity was thrombocytopenia (n = 14, 35%) while neutropenia (n = 3, 7.5%) and anaemia (n = 10, 25%) were less common (Table 3). Grade 3/4 thrombocytopenia was noted in 4 patients in which Nilotinib dose reductions was attempted however 2 patients needed Nilotinib discontinuation due to persistent grade 3/4 thrombocytopenia and in 2 patients Nilotinib was continued as lower dose (200 mg BD) with optimal response. Twenty two patients (55%) experienced some grade of hyperbilirubinemia but grade 3 hyperbilirubinemia was seen in only 6 (15%) patients and none had grade 4. Hyperbilirubinemia was predominantly unconjugated and was associated with normal liver enzymes except in one patient with grade 2 AST elevation. Grade 3 hyperbilirubinemia was managed with intermittent use of ursodeoxycholic acid and no patient required Nilotinib discontinuation for hyperbilirubinemia. Other toxicities noted were new onset hyperlipidemia in three patients (7.5%) and new onset diabetes mellitus in one patient (2.5%). Routine pancreatic enzyme (amylase and lipase) testing was not done during follow up however symptomatic pancreatic dysfunction was not noted in any patient. Electrocardiographic plots for at least one

Table 2. Treatment Characteristics and Outcome of Patients Started on First Line Nilotinib

Characteristics	N (%)	Median (Range)
Starting dose of Nilotinib per day (mg)		
· 800	6 (15)	
· 600	34 (85)	
Dose reduction required (number of patients, %)	4 (10)	
Follow up duration in months (Median, Range)		17 (7-79)
Response at 3 months (evaluable 40/40)		
· EMR, BCR-ABL1 ≤ 10%	33 (82.5)	
· BCR-ABL1 ≤ 1%	14 (35)	
· MMR, BCR-ABL1 ≤ 0.1%	4 (10)	
· MR4, BCR-ABL1 ≤ 0.01%	NIL	
Response at 12 months (evaluable 33*/40)		
· BCR-ABL1 > 1% (Failure)	5 (12.5)	
· BCR-ABL1 ≤ 1%	28 (84.8)	
· MMR, BCR-ABL1 ≤ 0.1%	14 (42.4)	
· MR4, BCR-ABL1 ≤ 0.01%	7 (21.2)	
Nilotinib Discontinued (in number of patients, %)	4 (10)	
Reasons for Nilotinib Discontinuation		
· Intolerance (Thrombocytopenia)	2 (5)	
· Failure/Progression	2 (5)	

EMR, Early Molecular Response which is generally defined as BCR-ABL ≤ 10% at 3 months of 1st line TKI initiation, MMR (Major Molecular Response) is defined as BCR-ABL1 transcript level ≤0.1%, MR4 is defined as BCR-ABL1 transcript level ≤0.01%. *Three patients discontinued Nilotinib before 12 months and 4 patients had follow up of less than 12 months.

Table 3. Shows Haematological and Non Haematological Adverse Events in Patients Treated with 1st Line Nilotinib (n = 40). NCI CTCAE v5.0

Adverse effects	All Grade, n (%)	Grade 3 - 4, n (%)
Thrombocytopenia	14 (35)	4 (10)
Anemia	10 (25)	0 (0)
Neutropenia	3 (7.5)	2 (5)
ALT/AST elevation	3 (7.5)	1 (2.5)
Bilirubin elevation	22 (55)	6 (15)

time point were available for 22 patients (55%) and no abnormalities were detected. New onset hypertension was noted in one (2.5%) patient and other symptomatic cardiovascular events were not noted.

Nilotinib as second line therapy in CML after Dasatinib

Fourteen patients received Nilotinib as second line TKI after dasatinib (generic or bio similar) failure or intolerance. The median age of this population was 37 years (range, 27–66 years), of whom 5 (35.7%) were male and rest female. Eight (57.1%) patients were in CML-AP and 6 (42.9%) in CML-CP at diagnosis. Ten patients (71.5%) were in EUTOS High Risk Group at diagnosis and 4 (28.5%) in Low risk group.

Median duration of exposure to dasatinib among all 14 patients was 9 months (range 2-42 months). Reason for change to Nilotinib was failure in 5 (35.7%) patients, intolerance in 7 (50%) patients and intolerance as well as failure in 2 (14.2%) patients. Among total of 9 patients who had intolerance with or without failure, four (44.4%) had persistent grade 2 or 3 diarrhoea, three (33.3%) had recurrent or persistent cytopenias and two (22.2%) had cytopenia as well as diarrhoea. TKD mutation analysis was done only in one patient prior to change in TKI and it was negative.

Median duration of follow up of these patients on Nilotinib was 20 months (range 6-54 months). At 3 months a total of 12 (85.7%) patients achieved a BCR-ABL1 level of ≤10% whereas one (7.1%) patient failed to achieve a BCR-ABL1 level of ≤10% (Table 4). One patient (7.1%) was not in CHR at 3 months and hence RQ-PCR was not done. This patient progressed to blast crisis and expired at 6 months of follow up. At 12 months analysis 5 (38.4%) patients were labelled as failure (BCR-ABL1 > 1%) however 2 of these patients were on reduced dose Nilotinib (150 mg BD) in view of grade 3/4 cytopenias. Three of these 5 patients were continued on Nilotinib as there BCR-ABL1 was near 1% (range 1.34-2.25) including one patient on reduced dose Nilotinib. Two of these 5 patients were switched back to dasatinib (TKD mutation was not done) in view of limited options of affordable TKIs. MMR and MR4 rates at 12 month was 46.1% and 23.1% respectively.

The most common haematological toxicity was thrombocytopenia (n = 6, 42.8%) while neutropenia (n = 1, 7.1%) and anaemia (n = 5, 35.7%) were less common. Grade 3/4 hematological toxicity was noted in 3 patients in whom Nilotinib dose reduction was attempted (150 mg BD). Among these three patients on reduced dose Nilotinib, one patient progressed to blast crisis (expired) and 2 patients showed suboptimal

Table 4. Treatment Characteristics and Outcome of Patients Started on Second line Nilotinib after Dasatinib Failure/ Intolerance. (n = 14)

Characteristics	N (%)	Median (Range)
Starting dose of Nilotinib per day (mg)		
· 800	5 (35.7)	
· 600	9 (64.2)	
Dose reduction required (number of patients, %)	3 (21.4)	
Follow up duration after starting Nilotinib (in months)		20 (6-54)
Response at 3 months on Nilotinib (evaluable 14/14)*		
· Not in CHR	1 (7.1)	
· EMR, BCR-ABL1 ≤ 10%	12 (85.7)	
· BCR-ABL1 ≤ 1%	8 (57.1)	
· MMR, BCR-ABL1 ≤ 0.1%	4 (28.5)	
· MR4, BCR-ABL1 ≤ 0.01%	1 (7.1)	
Response at 12 months (evaluable 13/14)*		
· BCR-ABL1 > 1% (Failure)	5 (38.4)	
· BCR-ABL1 ≤ 1%	8 (61.5)	
· MMR, BCR-ABL1 ≤ 0.1%	6 (46.1)	
· MR4, BCR-ABL1 ≤ 0.01%	3 (23.1)	
Nilotinib Discontinued (in number of patients, %)	3 (21.4)	
Reasons for Nilotinib Discontinuation		
· Failure/Progression	3 (21.4)	

EMR, Early Molecular Response which is generally defined as BCR-ABL ≤ 10% at 3 months of 1st line TKI initiation, MMR (Major Molecular Response) is defined as BCR-ABL1 transcript level ≤0.1%, MR4 is defined as BCR-ABL1 transcript level ≤0.01%. *One patient had no CHR in peripheral blood sample at 3 months of follow up and hence RQ-PCR was not done. This patient progressed to Blast crisis and expired hence excluded from 12 months analysis.

response at 12 months. Four patients (28.5%) experienced hyperbilirubinemia but grade 3/4 hyperbilirubinemia was seen in none of the patients. Other toxicities noted were new onset hyperlipidaemia in one patients (7.1%).

Nilotinib as second line therapy in CML after Imatinib

Fifty-one patients received Nilotinib as second line TKI after Imatinib (generic or bio similar) failure or intolerance. The median age of this population was 46 years (range, 19–68 years). Other demographic details and baseline parameters are described in Table 5.

Median duration of exposure to Imatinib among all 51 patients was 13 months (range 4-168 months). Reason for change to Nilotinib was failure in 43 (84.3%) patients, intolerance in 1 (1.9%) patients and intolerance as well as failure in 7 (13.7%) patients. Disease status in terms of CHR and RQ PCR BCR/ABL levels at the time of TKI switch from Imatinib to Nilotinib is shown in table 6. TKD mutation analysis was done in 22 (43.1%) patient prior to change in TKI. Mutations detected were singly occurring missense mutations (n = 4) and insertions and deletions without point mutations (n = 3) and remaining 15 (68.2%) cases were negative for any TKD mutation. Singly occurring missense mutations seen were Q252X, E459K, H396R and T315I (one in each patient). Insertions and deletions without point mutation seen was 185bp deletion in exon 7 of the ABL KD (p.R362fs*21/c.1086_1270del185) in 3 patient. The patient with T315I mutation was switched to hydroxyurea as mutation report came and he is currently alive and in CHR. Patient with Q252X and E459K mutations achieved MR4 (BCR/ABL= 0.005%) and optimal response (BCR/ABL = 0.159%) respectively at 12 months follow up. Patient with H396R mutation failed on Nilotinib (BCR/ABL = 5.399% at 36 months) and hence was switched to dasatinib and he also failed on dasatinib (BCR/ABL = 6.15% at 12 months) and is being continued on Dasatinib. One patient with 185bp deletion progressed to blast crisis (B-Lymphoid) at 27 months of follow up on Nilotinib, one patient failed Nilotinib (BCR/ABL = 8.36% at 36 months) and was switched to Dasatinib. Remaining one patient (total 3 with 185bp deletion) achieved MR4 (BCR/ABL = 0.008% at 24 months).

Median duration of follow up of these patients on Nilotinib was 24 months (range 3-84 months). Three month BCR-ABL evaluation was done in 49 patients (out of 51). One patient progressed to blast crisis and other had nilotinib intolerance (grade 4 thrombocytopenia) and Nilotinib was discontinued without BCR-ABL evaluation (n = 2). Out of 49 patients, 36 (73.5%) patients achieved a BCR-ABL1 level of ≤ 10% at 3 months. Twelve month BCR-ABL evaluation was done in 42 patients (out of 51). Nine patients had follow up duration on Nilotinib of less than 12 months. In these 9 patients Nilotinib was discontinued before 12 months because of failure or progression. Among evaluable patients at 12 months (n = 42), 32 (76.2%) patients achieved optimal response of BCR-ABL1 ≤ 1%. (Table 7).

The most common haematological toxicity was thrombocytopenia (n = 25, 49.2%) while neutropenia

Table 5. Characteristics of Patients who Were Started on 2nd Line Nilotinib after Imatinib Failure/Intolerance (n = 51)

Baseline Characteristics (at diagnosis)	N (%)	Median (Range)
Age, Median (range)		46 (19-68)
>40 years	31 (60.7)	
<40 years	20 (39.3)	
Sex		
· Male	27 (52.9)	
· Female	24 (47.1)	
Disease Phase		
· Chronic Phase	46 (90.1)	
· Accelerated Phase	5 (9.9)	
Baseline Laboratory values (at diagnosis)		
· Hb gm/dL, median (range)		10.2 (5.9-14.5)
· White blood cells (× 10^9/L), median (range)		163.8 (3.5-730.3)
· Platelet count (× 10^9/L), median (range)		305 (54-1970)
· Peripheral blood blasts (%), median (range)		2 (1-18)
· Bone marrow blasts(%), median (range)		4 (2-18)
· Basophils (%), median (range)		10 (1-22)
Spleen (bcm), median (range)		7 (0-20)
EUTOS Risk Score, median (range)		90 (37-193)
EUTOS Risk group		
· High Risk	28 (54.9)	
· Low Risk	23 (45.1)	

EUTOS, European Treatment and Outcomes Study (EUTOS) Score

(n = 3, 5.8%) and anaemia (n = 15, 29.4%) were less common. Grade 3/4 haematological toxicity (thrombocytopenia) was noted in 7 (13.7%) patients. Grade 3 anaemia was concomitant in 3 (5.8%) of these 7 patients and grade 3 neutropenia in 1 (1.9%) patient. Nilotinib dose interuptions for 10-14 days was done in these 7 patients and only one patient required dose reduction (200 mg BD) while others were restarted and continued on initial dose (300 mg BD or 400 Mg BD). Twenty one (41.2%) experienced hyperbilirubinemia (predominantly indirect) however grade 3 hyperbilirubinemia was seen in only 4 (7.8%) patient and none of the patients had grade 4 hyperbilirubinemia. None of the patient required dose interruption for hyperbilirubinemia and responded to use of ursodeoxycholic acid. Other toxicities noted were new onset hyperlipidaemia in 5 patients (9.8%) and new onset diabetes mellitus in 3 patient (5.8%).

At median follow up of 24 months (range 3-84 months), Nilotinib was discontinued in 16 (31.3%) patients. Predominant reason for discontinuation was Nilotinib failure (Table 7). Median duration of Nilotinib exposure before discontinuation was 12 months (range 3-50 months). Three patients progressed to blast crisis (Myeloid blast crisis in 2 patients and B-Lymphoid blast crisis in 1 patient) while on Nilotinib. One patient with myeloid blast crisis expired.

Nilotinib as Third line therapy in CML after Imatinib and Dasatinib

Twenty patients received Nilotinib as third line TKI after Imatinib and Dasatinib (generic or bio similar) failure or intolerance. The median age of this population was 48 years (range, 17–70 years). Ten were male (50%) and rest were female. All 20 (100 %) patients were in CML-CP at diagnosis. Twelve patients (60%) were in EUTOS High Risk Group at diagnosis. All patients after failure of 2nd line TKI were counselled for need of Allo HSCT however due to logistic and financial issues these patients were continued on 3rd line agents and Allo HSCT referral or referral for compassionate basis asciminib was made after failure of 3rd line agent only.

All of these patients were first started on Imatinib and then switched to 2nd line dasatinib after a median interval of 9 months (range 1-95 m). Dasatinib to 3rd line nilotinib switch was made at median interval of 9 months (range 1-24 months). Median duration of TKI exposure before starting Nilotinib was 24 months (range 12-112 months). Imatinib to 2nd line Dasatinib switch was mainly because of Imatinib failure [17 patients (85%) as depicted in Table 8. Dasatinib to 3rd line Nilotinib switch was for Intolerance & failure in 9 (45%) patients and intolerance in 6 (30%) patients. Among 15 (75%) patients with dasatinib intolerance with without failure, five (33.3%) had recurrent pleural effusion, one (6.6%) had pericardial effusion, three (19.8%) had grade 3 or 4 diarrhoea, five (33.3%) had cytopenias requiring dose reduction and interuptions. One (6.6%) patient had pyrexia of unknown origin for which extensive workup didn't reveal any cause however switch to Nilotinib resulted in resolution in fever.

Median duration of exposure to 3rd line Nilotinib in was 20 months (range 12-38 months). Disease status in terms of CHR and RQ PCR BCR/ABL levels at the time

Table 6. Reason for Change from Imatinib to Nilotinib

Reason for Change from Imatinib to Nilotinib*	N (%)
· Intolerance	1 (1.9)
· Failure	43 (84.3)
Not in CHR	5 (11.6)
BCR-ABL1 > 10%	25 (58.1)
BCR-ABL1 1-10%	13 (30.2)
· Failure/Intolerance#	7 (13.7)
Not in CHR	1 (14.2)
BCR-ABL1 > 10%	4 (57.1)
BCR-ABL1 1-10%	2 (28.5)

*Median duration of exposure to Imatinib was 13 months (range 4-168 months). #Patients who were having intolerance and frequent dose reductions and interruptions.

Table 7. Treatment Characteristics and Outcome of Patients Started on Second Line Nilotinib after Imatinib Failure/ Intolerance. (n = 51)

Characteristics	N (%)	Median (Range)
Starting dose of Nilotinib per day (mg)		
· 800	23(45.1)	
· 600	28 (54.9)	
Dose reduction required (number of patients, %)	5 (9.8)	
Follow up duration in months (Median, Range)		24 (3-84)
Response at 3 months (evaluable 49/51)*		
· BCR-ABL1 ≤ 10%	36 (73.5)	
· BCR-ABL1 ≤ 1%	19 (38.8)	
· MMR, BCR-ABL1 ≤ 0.1%	4 (7.8)	
· MR4, BCR-ABL1 ≤ 0.01%	NIL	
Response at 12 months (evaluable 42/51)#		
· BCR-ABL1 > 1% (Failure)	10 (23.8)	
· BCR-ABL1 ≤ 1%	32 (76.2)	
· MMR, BCR-ABL1 ≤ 0.1%	16 (38.1)	
· MR4, BCR-ABL1 ≤ 0.01%	6 (14.3)	
Nilotinib Discontinued (in number of patients, %)	16 (31.3)	
Reasons for Nilotinib Discontinuation		
· Intolerance (Thrombocytopenia)	1 (1.9)	
· Intolerance/Failure	2 (3.8)	
· Failure/Progression (all cases)	13 (25.4)	
· Progression to CML-Blast crisis	3 (5.7)	

EMR, Early Molecular Response which is generally defined as BCR-ABL ≤ 10% at 3 months of 1st line TKI initiation, MMR (Major Molecular Response) is defined as BCR-ABL1 transcript level ≤0.1%, MR4 is defined as BCR-ABL1 transcript level ≤0.01%. *Two patients discontinued Nilotinib on or before 3 months and hence BCR/ABL RQ PCR was not done @ 3 months. #Nine patients had follow up duration on Nilotinib of less than 12 months.

of TKI switch from dasatinib to Nilotinib is shown in table 8. TKD mutation analysis was done in 12 (60%) patient prior to change in TKI to Nilotinib. Singly occurring missense mutation E355A was detected in one patient (8.3%) and 185bp deletion in exon 7 of the ABL KD (p.R362fs*21/c.1086_1270del185) was detected in one (8.3%) patient. Other 10 (83.3%) patients were negative for TKD mutation.

Out of 20 patients, 13 (65%) patients achieved a BCR-ABL1 level of ≤ 10% and 8 (40%) patients achieved a BCR-ABL1 level of ≤ 1% at 3 months of Nilotinib initiation. At 12 months 8 patients (40%) patients qualified as failure as per ELN guidelines [19]. Out of these 8 patients 4 (50%) patients were on low dose nilotinib (200 mg BD) for their nilotinib intolerance (cytopenias). Out of these 8 patients, one (12.5%) was switched to hydroxyurea, one (12.5%) was switched to bosutinib, 2 (25%) were continued on full dose nilotinib and 4 (50%) were continued on low dose nilotinib (Table 9). At last follow up all patients were alive.

The most common haematological toxicity was thrombocytopenia (n = 9, 45%) while neutropenia (n = 3, 15%) and anaemia (n = 5, 25%) were less common. Grade 3/4 haematological toxicity (thrombocytopenia) was noted

Table 8. Reason for TKI Switch to Nilotinib as 3rd Line.

Reason for TKI Switch	Imatinib to Dasatinib	Dasatinib to Nilotinib
· Intolerance	2 (10)	6 (30)
· Failure	17 (85)	5 (25)
Not in CHR	NIL	NIL
BCR-ABL1 > 10%	9 (52.9)	5 (100)
BCR-ABL1 1-10%	8 (47.05)	NIL
· Failure/Intolerance#	1 (5)	9 (45)
Not in CHR	NIL	NIL
BCR-ABL1 > 10%	1 (100)	7 (77.7)
BCR-ABL1 1-10%	NIL	2 (22.2)

#Patients who were having intolerance and frequent dose reductions and interruptions.

Table 9. Treatment Characteristics and Outcome of Patients Started on Third Line Nilotinib after Imatinib and Dasatinib Failure/Intolerance. (n = 20)

Characteristics	N (%)	Median (Range)
Starting dose of Nilotinib per day (mg)		
· 800	14(70)	
· 600	6 (30)	
Dose reduction required (number of patients, %)	5 (25)	
Follow up duration in months (Median, Range)		20 (12-38)
Response at 3 months (evaluable 20/20)		
· BCR-ABL1 ≤ 10%	13 (65)	
· BCR-ABL1 ≤ 1%	8 (40)	
· MMR, BCR-ABL1 ≤ 0.1%	3 (15)	
· MR4, BCR-ABL1 ≤ 0.01%	2 (10)	
Response at 12 months (evaluable 20/20)		
· BCR-ABL1 > 1% (Failure)	8 (40)	
· BCR-ABL1 ≤ 1%	12 (60)	
· MMR, BCR-ABL1 ≤ 0.1%	8 (40)	
· MR4, BCR-ABL1 ≤ 0.01%	3 (15)	
Nilotinib Discontinued (in number of patients, %)	2 (10)	
Nilotinib continued at low dose (in number of patients, %)	4 (20)	
Reasons for Nilotinib Discontinuation		
· Failure	2 (10)	

EMR, Early Molecular Response which is generally defined as BCR-ABL ≤ 10% at 3 months of 1st line TKI initiation, MMR (Major Molecular Response) is defined as BCR-ABL1 transcript level ≤0.1%, MR4 is defined as BCR-ABL1 transcript level ≤0.01%.

in 4 (20%) patients. Grade 3 anaemia was concomitant in 2 (10%) of these 4 patients and grade 3 neutropenia in 2 (10%) patient. Nilotinib dose interuptions for 10-14 days was done in 5 patients and 4 patient required continuation on low dose nilotinib (200 mg BD) while one was continued on initial dose (400 Mg BD). Thirteen patients (65%) experienced hyperbilirubinemia (predominantly indirect) however grade 3 hyperbilirubinemia was seen in only 3 (15 %) patient and one patient (5%) had grade 4 hyperbilirubinemia. Extensive work up didn't reveal any other cause in patient with grade 4 hyperbilirubinemia (Maximum Total Bilirubin 7.5 mg/dl) and it was considered drug (nilotinib) induced. Dose reduction to 200 mg BD lead to resolution of this issue and hence patient was continued on same dose. Two patients (10%) developed hypertriglyceridemia during follow up and required antihyperlipidemic drugs.

Overall summary of safety and efficacy of Nilotinib

One hundred twenty six patients were started on Nilotinib as first or later lines of therapy. At 12 months of follow up, 108 patients were eligible for BCR/ABL analysis. Eighteen patients were excluded from analysis as 13 patients had follow up duration of less than 12 months and 5 patients discontinued nilotinib before 12 months. Out of 108 patients, 80 (74.1%) patients achieved BCR/ABL of ≤ 1% at 12 months. MMR and MR4 at 12 months was seen in 44 (40.7%) and 19 (17.6%) patients respectively. Twenty five patients (19.8%) discontinued nilotinib. Reason for discontinuation was nilotinib failure in 20 (15.8%) patients, intolerance (cytopenia) in 3 (2.3%) patients and intolerance as well as failure in 2

(1.6%) patients. A total of five (3.9%) patients progressed to blast crisis while on nilotinib and 2 (1.6%) of them expired. The most common haematological toxicity was thrombocytopenia of any grade seen in 54 (42.8%) patients. Twenty three 23 (18.2%) had grade 3/4 thrombocytopenia. Nilotinib discontinuation was required in 4 patients with persistent grade 4 thrombocytopenia. Hyperbilirubinemia (indirect) without significant AST/ALT elevation was seen in 60 (47.6%) patients. Grade 3 hyperbilirubinemia was seen in in 13 (10.3%) patients and grade 4 in 1 (0.8%) patient.

Discussion

This study represents one of the largest cohort of CML-CP and CML-AP patients who were treated with Nilotinib as first line and later lines of therapy from India. Generic Imatinib and Dasatinib are available in India at monthly expense of USD 10 and 40 respectively and hence preferred choice of TKI and is commonly used as 1st and 2nd line TKI in CML. Nilotinib at a monthly cost of 96 USD (with patient support program) is costlier than other two options which limits it use in LMIC contries like India.

Till date only two small studies have reported its safety and efficacy in Indian patients. Singh et al reported use of 1st line Nilotinib in 37 patients and Manuprasad et al reported its use as 2nd line TKI in 37 patients [18, 17].

Registration trails for 1st line nilotinib have shown MMR rate of 51% with Nilotinib 300 mg BD [14]. ENESTchina trail which was a phase 3 nilotinib vs imatinib trial in newly diagnosed CML patients reported MMR of 52.2% at 12 months [20]. Other real world studies have shown MMR rates as high as 73% at 12 months [21]. Only other retrospective Indian study in this setting had reported MMR rate of 71.5% at 12 months [18]. In our study 42.4% patients achieved MMR at 12 months in 1st line Nilotinib. Drug compliance is unlikely to be reason in our study of lower MMR rates as drug compliance was ensured with help of medical social workers. Registration trial for 2nd line nilotinib had shown that at 6 months of follow up, complete cytogenetic response was achieved in 28% of patients [22]. MMR rates were not reported in this study. Real world data from Taiwan showed that MMR was achieved in 39.7% patients at 12 months on 2nd line Nilotinib [23]. In our patient cohort using nilotinib as 2nd line TKI, 38.1 % patients achieved MMR at 12 months in patients with imatinib failure or intolerance and 46.1% patients achieved MMR at 12 months in patients with dasatinib failure or intolerance. In the study of the Giles et al. [24], the authors evaluated 60 patients with CML (39 in CP and 21 in AP) who received third-line nilotinib. Complete cytogenetic response (CCyR) was achieved in 24% and MMR rates were not reported. Several other studies which reported outcomes with third line nilotinib has shown MMR rates of 15-20% at 12-21 months [25, 26]. In our study MMR rate at follow up of 12 months was 40%.

Side effect profile observed in our study was similar as reported in earlier studies [16, 22, 27]. Thrombocytopenia was most common haematological adverse effect as seen in 54 (42.8%) patients including twenty three 23 (18.2%) patients with grade 3/4 thrombocytopenia. Hyperbilirubinemia (indirect) without significant AST/ALT elevation was most commonly seen non haematological side effect in 60 (47.6%) patients. We noted a relatively higher frequency of all grade hyperbilirubinemia in our patients however grade 3/4 hyperbilirubinemia incidence was comparable to incidence reported from the West [16, 22]. Extensive work up didn't reveal any other cause in patient with grade 3/4 hyperbilirubinemia and it was considered drug (nilotinib) induced. This is likely an effect of pharmacogenomic profile of nilotinib in Indian patients. The other major concern with nilotinib is cardiovascular toxicity which was not observed within the short follow-up period. Our study is a retrospective analysis and hence grade 1 and 2 side effects are less likely to be represented.

Nilotinib discontinuation rates in 1st line use was reported as 16% and 18% with dose of 300 BD and 400 BD respectively at 12 months by Saglio et al [16]. Two major cause for discontinuations reported were adverse effects and suboptimal response. ENESTchina trail reported nilotinib discontinuation rate of 13.4% at 24 months follow up [20]. In our study nilotinib discontinuation was seen in 4 (10%) patients at median follow up of 17 months in 1st line nilotinib setting (2 due to adverse effect and 2 due to suboptimal response). Higher discontinuation rates have been reported in 2nd line Nilotinib setting. Discontinuation rate of 48% was reported in the ENACT study and 61% in the registration study [14, 27, 28, 29]. In real world scenario discontinuation rates of 36.5% was reported in a study from Taiwan, although only 4.7% of the patients discontinued due to adverse effects, while 16.5% discontinued due to unsatisfactory therapeutic effect [23]. In our study nilotinib discontinuation was seen in 31.1% patients (2nd line after imatinib) and 21.1% patients (2nd line after dasatinib). Suboptimal response or progression was major cause of nilotinib discontinuation in 84.2% of these patients. In 3rd line nilotinib setting discontinuation rate of 10% was noted. Overall, our study shows that nilotinib discontinuations are predominantly because of suboptimal response or progression of disease. Among discontinuations due to adverse effect grade 4 thrombocytopenia was major cause. Hyperbilrubinemia is a common side effect of nilotinib however none of the patient required drug discontinuation. One patient required dose reduction by 50% which lead to resolution of grade 4 hyperbilirubinemia.

In conclusion, our study demonstrates that treatment with nilotinib was well-tolerated in Indian patients and was effective in achieving molecular remission rates in 1st, 2nd or 3rd line therapy in the real-world setting. Safety and efficacy were in line with published western or Asian studies.

Acknowledgments

Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of

author affiliated Institute .

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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