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Original Research Article

Experience with Nilotinib in Chronic Myeloid Leukemia-A Retrospective Analysis of Clinical Outcome

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ABSTRACT

Background: Nilotinib is a selective and potent second generation tyrosine kinase inhibitor useful in treatment of chronic myeloid leukemia (CML). There is scarcity of data on its efficacy and safety in Indian population. Purpose of the study is to determine the clinical efficacy and adverse events (AEs) of nilotinib when used as second line treatment of CML.
Methods: This retrospective analysis was conducted at a regional cancer center in western India. CML patients with either imatinib failure or intolerance and treated with nilotinib were analyzed. Clinical outcome like hematological, cytogenetic and molecular response were reported. The frequency of AEs was assessed. Overall survivals of patients were calculated.
Results: Total 48 patients were evaluated. Median age of the patient was 45 years. There were 46 (95.83%) patients in chronic and 2(4.17%) in accelerated phase at time of treatment. Median duration of imatinib therapy was 60 (range, 3-175) months. Mean white blood cell count at time of starting treatment was 60277/µl. Imatinib resistance bcr-abl mutation was detected in 15.56% of patients. Overall, non-hematological (18.75%) and hematological (12.5%) AEs were observed in31.25% of patients. Non-laboratory AEs were electrocardiogram abnormality (6.25%), skin rash (4.17%) and gastric intolerance (2.08%). Laboratory abnormalities (grade 3 or above) were thrombocytopenia (12.5%), pancytopenia (10.42%), asymptomatic transaminitis (2.08%) and renal failure (2.08%). Overall, 82.14% patients achieved CHR with nilotinib. Median duration of exposure to nilotinib was 8.5 (range, 1–72) months. We observed 2 (4.17%) deaths. Majority (95.83%) patients were alive at time of analysis. Median overall survival was 74 (range, 5-187) months.
Conclusions: Nilotinib is safe and effective second line therapy for CML in Indian patients. Although, this is a small study with relatively short follow up, the difference made by nilotinib in progressive disease (despite high dose of imatinib) and its tolerability is worth reporting.

Keywords: Chronic Myeloid Leukemia, Nilotinib, Retrospective analysis

INTRODUCTION

Nilotinib is a selective and potent second generation tyrosine kinase inhibitor (TKI).It is active in imatinib resistant or intolerant patients with CML-CP or AP. [1, 2] In India, imatinib is the standard of care for first line therapy. [3,4] Although data from randomized trials suggest that first line use of second generation TKIs can lead to faster and deeper molecular responses, [5-8] the

higher cost limits their use in newly diagnosed patients. Nilotinib and dasatinib are the two second generation TKIs currently available in the India but there are few reports detailing its use in Indian patients. [9,10] Herein, we report a preliminary experience of clinical outcome and tolerability of nilotinib as second line therapy in adult CML.

METHODS

This is a retrospective analysis conducted at single regional cancer centre in western India. All CML patient case files from Jan 2017 to April 2019 were scanned and patients who were found to be on nilotinib during that period were selected and their retrospective data was recorded. CML-CP or AP patients above 18 years of age treated with nilotinib as second-line TKIs following imatinib resistance or intolerance were evaluated. Patients with CML-blast crisis (BC) were excluded. Imatinib failure [11] was defined as failure to reach response milestones or any sign of loss of response defined as haematologic or cytogenetic relapse, rising transcript after achieving major molecular response (MMR) if associated with loss of cytogenetic response or disease progression to AP or BC. [11] Imatinib intolerance [12] was considered as if imatinib therapy discontinued because of grade 3 or above AEs that persisted despite optimal supportive care measures, or experienced grade 2 AEs related to imatinib therapy that persisted for >1 month or that recurred >3 times, whether the dose was reduced or discontinued. [12]

Clinical data were obtained from the patients' medical records. Detailed history was reviewed for duration of diagnosis, response and tolerance of imatinib treatment, compliance, dose escalation if done, indication of nilotinib treatment, imatinib resistance mutation analysis using RT-PCR if done and white blood cell (WBC) count at time of starting nilotinib. Patients underwent complete blood count, liver and renal function tests, serum electrolytes, random blood sugar, electrocardiogram (ECG) prior to starting nilotinib and periodically thereafter. All patients were started on nilotinib at dose of 400mg twice daily except those with prior hematological intolerance to imatinib therapy; the dose of nilotinib was 600 mg. For grade 3 or above toxicity, nilotinib was withheld and restarted at a lower dose. Nilotinib was halted in patients who couldn't tolerate at least 200 mg per day. Patients were followed with clinical examination, complete blood counts and relevant laboratory investigations as per physician's discretion. Clinical data of response to nilotinib i.e. complete haematologic response (CHR), cytogenetic response (CyGR) and MMR were captured whenever available. Response to therapy was defined according to O'Brien [13] et alfor CP and Talpaz [14] et al for AP. Toxicity data recorded in case files was captured and grading of toxicity was performed according to CTCAE 4.0. [15]

Statistical analysis: Microsoft excel 2007 spreadsheet was used for data entry and analysis. The results were reported as the mean or median for quantitative variables, such as age, WBC count and disease duration. The results are presented as number and frequency (percentage) for qualitative variables, such as gender, CHR, CyGR, and AEs. Rates of CHR and response rates were compared using a chi-square analysis. PFS was defined as the time from the start of nilotinib to the earliest date of hematologic progression or disease progression (AP/BC) or death from any cause during treatment. Overall survival (OS) was calculated from the start of imatinib therapy until death due to any cause. Total duration of treatment with imatinib and nilotinib were included.

RESULTS

Patient characteristics: Total 48 CML patients on nilotinib as second line TKI following imatinib failure or intolerance

were analyzed. The baseline characteristics of patients are shown in Table I.

Table1: Baseline characteristics of patients

Characteristics	Value
Number (no.)	48
Median age (year), (range)	45 (18-68)
Gender male/female, ratio	29/19, 1.5:1
Median disease duration, month (range)	60 (3-175)
Disease phase at time of imatinib therapy,no. (%) Chronic Accelerated	 48(100) 00(0)
Disease phase at time of nilotinib, no. (%) Chronic Accelerated	 46 (95.83) 02 (4.17)
Prior imatinib therapy duration(month), median (range) Duration in years, % (no.) < 2 2-<5 5-10 >10	60 (3-175) 22.92(11) 29.17(14) 20.83(10) 27.08(13)
Imatinib resistance, no. (%)	44 (91.66)
Imatinib intolerance, no. (%)	04 (8.33)
Imatinib dose: 600-800 mg, no. (%)	41 (85.41)
ABL kinase domain mutation, no. (%)	7/45 (15.56)
Response of imatinib therapy % (no. with data) Complete hematologic response Complete cytogenetic response Major molecular response Progressive disease Primary refractory disease	 95.83(46/48) 80.44(12/37*) 33.33(4/12*) 4.17(2/48) 4.17(2/48)
Pre nilotinib white cell count(µl), mean(range)	60277(range, 2300–380,000)

The median age was 45 (range, 18-68) years with a male predominance over female at the ratio of 1.5:1 respectively. All patient were in CML-CP at the time of initial diagnosis while 46 (95.83%) patients in CML-CP and 2 (4.17%) were in CML-AP at the time of initiation of nilotinib. The median duration from CML diagnosis to initiation of nilotinib was 5 years (3-175months). Five patients had medical co morbidities like diabetes mellitus, hypothyroidism, old cerebrovascular accident and ischemic heart disease. The median duration of imatinib therapy was 60 (range, 3-175) months. Twenty five (52.08%) patients received imatinib for less than 5 years, while 23(47.91%) for more than 5 years. Imatinib therapy was initiated at 400mg dose but subsequently dose was escalated to 600mg (n=7, 14.58%) to 800mg (n=34, 70.83%) due to suboptimal response or loss of response. Dose was reduced to 300 mg due to intolerance in 2(4.17%) patients. Five (10.42%) patients had imatinib dose of 400mg at the time of nilotinib treatment. Prior best response to imatinib therapy was CHR in 46 (95.83%) and no CHR in 2(4.17%) patients. CyGR was achieved in 12 out of 37(32.43%) evaluable patients while in 9 data were not available. Major molecular remission was achieved in 4 out of 12 (33.33%) evaluable patients. Majority (91.66%) of patients received nilotinib due to imatinib failure. Thirty six (75%) patients had loss of response manifested as either hematological or cytogenetic or molecular relapse while 8 (16.67%) patients had suboptimal response despite dose escalation. Four (8.33%) patients received nilotinib due to imatinib intolerance (cytopenia=2, skin rash=2). Mean WBC count at the time of starting nilotinib treatment was 60277/µl(range, 2300–380,000/µl).

Outcome with nilotinib: Among 24 patients with hematological relapse, 21 achieved CHR while 3 did not achieve CHR. Among primary refractory disease (no CHR=2) and progressive disease (AP=2), half of them achieve CHR. So overall, 82.14% patients achieved CHR with nilotinib. Those with cytogenetic relapse or suboptimal CyGR 8 patients achieved CyGR.

Table 2: Outcomes of switching to nilotinib (n=48)

Reasons for switch to nilotinib	Total No. (%)	Responded as a result of switching No. (%)	No response No. (%)	Stopped due to toxicity No.
Intolerance to imatinib	4(8.33)	3 (75)	0	1
Not achieved CHR	2(4.17)	1(50)	1 (50)RD	0
Progressed to AP	2(4.17)	1(50)	1(50)	0
Loss of CHR	24(50)	21(87.5)	3(12.5)	0
Loss of CyGR/MMR	6(12.50)	2(33.33)†	N/A	1
No CyGR	10(20.83)	6(60)†	N/A	1

CHR, complete haematologic response, CyGR, cytogenetic response, MMR, major molecular response, AP, accelerated phase, RD, refractory disease, N/A, Not available, † available data

Imatinib resistance bcr-abl mutations were detectable in 7 (15.56%) out of 45 patients tested. None of them were had T315I. All 7 had hematological relapse. All except one achieved CHR, 1 is in MMR and 1 (M244V) patient progressed to blast crisis and died. Six patients are on treatment. Type of mutation and response to nilotinib is shown in Table 3.

Table 3: Types of imatinib resistance BCR-ABL mutations and response

Types of mutations	Clinical Response	Duration of follow up (months)
L387M	MMR	14
F317L	CHR	9
G250E	CHR	9
E255K	CHR	8
F486S	CHR	6
M351T	CHR	2
M244V	Progressed and died	7

CHR, complete haematologic response, MMR, major molecular response

Dose of nilotinib: Starting dose of nilotinib was 400 mg twice daily. Six (12.5%) patients required dose reduction during the treatment period. Three patients continued nilotinib at reduced doses (600mg, n=1 and 400mg, n=2). Three patients required permanent discontinuation due to recurrent and persistent thrombocytopenia (despite dose reduction), prolonged QTcF and renal failure 1 patient each. Two patients with cytopenia subsequently progressed to blast crisis and died. None of the patient died due to toxicity.

Toxicity: Overall, 31.25% of patients developed AEs. The non-hematological and hematological AEs were 18.75% and 12.5% respectively. Among non-laboratory AEs, ECG abnormality (n=3, 6.25%) was dominant followed by skin rash (n=2, 4.17%) and gastric intolerance (n=1, 2.08%). Among laboratory abnormalities, grade 3 or above hematologic AEs included thrombocytopenia (N=6, 12.5%) and pancytopenia (n=5, 10.42%). Isolated anemia, neutropenia and thrombocytopenia were observed in 1 patient each. Symptomatic transaminitis and azotemia was observed in 1(2.08%) patient each. No symptomatic pancreatic dysfunction or dyslipidemia was noted. None of the patients had worsening of diabetes. Three patients discontinued nilotinib, 1 due to rising serum creatinine despite stopping the drug and 2 had cytopenia with prolonged QTcF and multiple ventricular premature beats coexisting. There was no drug related death. Six patients needed dose modifications. Among patients who switched to nilotinib due to intolerance to imatinib therapy; activity of nilotinib was good. One patient with imatinib induced cytopenia had recurrent cytopenia with nilotinib and had to stop treatment. Those with imatinib induced skin rash did not show recurrence of skin lesion.

Follow up and current status: Median duration of exposure to nilotinib was 8.5 (range, 1–72) months. Thirty nine (81.25%) patients were on nilotinib at last follow-up (median duration 14, range, 4-34 months). Thirteen (33.33%) patients had completed more than 1 year of treatment. The median PFS is 81.25% and median OS is 74 (range, 5-187) months at median follow up of 8.5 months. Majority (95.83%) of patients are alive at the time of analysis.

All 39 (81.25%) patients on nilotinib are in CHR, 8 patients are in CyGR while 2 patients are in MMR. In remaining, data are not available as this is retrospective study;

short follow up duration and it is too early to look for CyGR or MMR. Nine (18.75%) patients discontinued treatment because of unsatisfactory results in 8 (4=refractory disease, 3=intolerance/toxicity and 1=progressive disease) and 1 patient was lost to follow up. Alternative treatment modalities were offered to those with progressive or refractory disease. One patient is on dasatinib, 2 patients are lost to follow up, 2 patients died due to blast crisis and 4 patients are on supportive care.

DISCUSSION

This is one of the few studies on the use of nilotinib as second line therapy in Indian patients. [9,10] At our centre, nilotinib is used in CML patients following imatinib failure or intolerance. It was possible to treat patients with nilotinib as drug is available under nilotinib patient assistance program and supported by government sponsored health scheme (fraction of cost is born by the government). The best approach to failure of imatinib therapy is to switch to a second-line TKIs when patient can afford the medicine. [11] The other option is to increase the dose of imatinib which may still improve the response in those patients who had suboptimal response. [16] Dose escalation was tried in majority of our patients. Forty one (85.42%) patients received 600 to 800 mg dose of imatinib before switching to nilotinib.

Our cohort had patients with advanced disease at the time of switching with median duration of CML diagnosis was of 5 years. Majority (54.17%) had completed 5 years of imatinib therapy, out of which 27.08% were on imatinib for more than 10 years. Prior duration of imatinib therapy of more than 5 years was associated with lower CHR with nilotinib as compared to less than 5 years of imatinib therapy however it was not statistically significant (Table 4).

A study by Maya KM [17] et al showed that the achievement of at least a CHR during imatinib treatment was predictive of a subsequent response to nilotinib, whereas a failure to achieve at least a CHR on imatinib therapy was predictive of progression or lack of response to nilotinib therapy. In her study,70% of patients whose best response to imatinib was a CHR, achieved at least a CHR to nilotinib, whereas 60% of patients without a CHR on imatinib did not achieve at least a CHR on nilotinib (P ¼ .0021). Of patients with a CHR as best response to imatinib, 40% had a CHR as their best response to nilotinib. [17] In current study, 87.50% patients with hematological relapse could achieve CHR while only 50% patients who did not achieve CHR with imatinib therapy did achieve CHR with nilotinib. However, results were not statistically significant (p value 0.157). Patients who did not achieve at least a CHR during imatinib therapy are less likely to respond to nilotinib and may do better with other TKIs or alternate treatment modality. [17]

Table 4: Factors predicting CHR to nilotinib therapy

Parameters	CHR with nilotinib, n(%)	No CHR with nilotinib, n (%)	Significance
CHR with imatinib therapy (n=24)	21(87.5)	03(12.5)	P value 0.157
No CHR with imatinib therapy (n=2†)	01 (50)	01(50)	x^2 =1.994
>5 years of imatinib therapy (n=19‡)	14(73.68)	05(26.32)	P value 0.815
< 5 years of imatinib therapy (n=9)	07(77.78)	02(22.22)	x^2 =.0546

CHR, complete haematological response, †Patient with accelerated phase or primary refractory disease were included as no CHR, ‡patients with only haematologiclal relapse were included

Data on the rate of achievement of cytogenetic or molecular response is not available for all patients. Among available data, 8 were tested with RQ-PCR, 6 are in CyGR and 2 (5.13%) patients are in MMR. Longer follow up may increase CyGR or MMR rates. [18]

Nilotinib treated patients may develop hyperbilirubinemia and transaminitis. Grade 3 or above hepatotoxicity was observed in 1%-5% in various studies. [8,10,19-20] An Indian study [10] reported to have 16% patients with hyperbilirubinemia. None of our patient had

hyperbilirubinemia but 1 patient developed grade 3 transaminitis which resolved with interruption of treatment. A study from China [21] reported to have grade 3 or above aspartate aminotransferase or alanine aminotransferase elevation in 0 and 3% respectively. Another study from South Asia [22] with an ethnically similar population from Pakistan did not have data on biochemical tests, so we don't know whether this is a genetic effect or not.

Nilotinib has been associated with prolonged QTc. [19-21] An Indian study [10] did not observe any ECG abnormality. Nicolani [19] et al observed 1 patient with low-grade QT prolongation. Wang [21] et al observed 9 patients (6.8%) in each arm having an absolute QTcF interval of 0.450ms; no patient had an absolute QTcF interval of 0.480ms. [21] In current study, asymptomatic ECG abnormality was observed in 3 patients. One patient had asymptomatic QTcF prolongation, while 2 developed multiple ventricular premature beats. Two of them have accompanying pancytopenia requiring discontinuation of treatment while 1 patient with premature beats resolved with supportive measures. This AE is more common in patients with a pre-existing cardiovascular risk factor and when nilotinib is prescribed as second line TKI. [23]

In current study, grade 3 or above hematologic AEs included thrombocytopenia (n=6, 12.5%) and cytopenia (n=5, 10.42%). The haematological side effect profile seen in the study was similar to earlier reports (table 5). The most common hematologic AE was thrombocytopenia, which led to discontinuation of drug use. [7,19,21-22] Saglio [7] et al reported thrombocytopenia more frequent in both nilotinib groups. Maya KM [17] et al reported haematological AEs in 40% patients on nilotinib therapy and were of grade 3 or above in 31%.The most common toxicities were thrombocytopenia (27%) and leucopenia(18%) and were of grade 3 or above in 13% and10% respectively. In a study by Wang [21] et al (by the 24 month cutoff), 68.4% of patients in the nilotinib experienced AEs leading to dose interruption or adjustment. The AEs most commonly leading to dose interruption or adjustment was thrombocytopenia (20.3%). Kantarjian [1] et al reported neutropenia (29%) and thrombocytopenia (29%) as the most frequent hematologic AEs. In study by Hussain [22] et al, 28.6% of patients had hematologic AEs; neutropenia (3.9%) was less frequent than thrombocytopenia (15.6%). Gurasova [18] et al showed that all newly occurring grade 3 or above hematologic abnormalities occurred within the first 2 months of therapy and with longer follow up the rate of AEs were relatively infrequent.

Table 5: Comparison of grade 3 or above toxicities of nilotinib in different studies

Studies	Current study n=48	Saglio et al [7] n=556	Manuprasad et al [10] n=37	Gurasova et al [18] n=37	Nicolini et al [19] n=1422	Wang et al [21] n=134	Hussain et al [22] n=82
Parameters	Number of patients (%)						
Anemia	1(2.08)	18 (3)	2 (5)	1 (3)	42 (3.5)	5(3.8)	–
Leucopenia	1(2.08)	60 (10)	3 (8)	5 (14)	35 (2.5)	13(9.8)	2 (2.4)
Thrombocytopenia	6(12.5)	61 (11)	9 (24)	8 (22)	308 (21)	34(25.6)	8 (10)
Renal failure	1(2.08)	0	N/A		0	0	N/A
Skin rash	3(6.25)	8 (1.4)	0 (0)	12 (32)	38 (2.7)	2(1.5)	2 (7)
Hyperbilirubinemia	N/A	21 (8)	6 (16)	5 (13)	59 (4.1)	6(4.5)	NA
Transaminitis AST/ALTs	1(2.08)	9/3	0	3(8%)	(2.1/0.8)	0/4(3)	NA
Prolonged QTcF	3(6.25)	0	0	0	0.3-1.3%	5(3.8)	0

ALT, alanine aminotransferase, AST, aspartate aminotransferase.

Nilotinib has been associated with pancreatitis and dyslipidemia. [20,24] However these complications were not observed in study population (pancreatic enzyme or lipid profile testing in asymptomatic patients was not done). None of the patients had symptomatic or significant hyperglycemia or worsening of

diabetes. One 65 years old female patient developed grade 3 elevations in serum creatinine; she was treated with imatinib for 7 years and was on 800 mg dose before shifting to nilotinib. She developed progressively rising serum creatinine despite stopping nilotinib and had to stop the drug. Tyrosine kinase inhibitor induced renal toxicity has been reported, though it is rare. Among TKIs, renal toxicity is more common with imatinib and less with dasatinib and nilotinib. [25] Nilotinib induced renal toxicity is very rare (<1%). [25] Those with pre-existing risk factor are more susceptible. In this case prior treatment with imatinib might be the reason apart from old age.

We noted a discontinuation rate of 18.75% (12.50%=no response to treatment and6.25% intolerable side effects). An Indian study [10] noted a striking discontinuation rate of 37%. Discontinuation due to AEs have been reported to occur in3%-15% patients in various other reports. [1,19,7,24] In current study, treatment related discontinuation were due to renal failure in 1 while 2 patients had cytopenia with prolonged QTcF and ventricular premature beats coexisting. There was no any treatment related casualty reported in the study. Overall, nilotinib was well tolerated. This is a retrospective analysis and so low grade AEs are less likely to be represented and low incidence of AEs might be because biochemical abnormality was not actively tested in asymptomatic patients.

The median PFS is 81.25% and median OS is 74 months at median follow up of 8.5 (range 1-72) months. There were only 2 deaths secondary to disease progression. Majority (95.83%) of the patients are alive at the time of analysis.

Limitations of the study are; it is retrospective, there was underreporting of both hematological and non-hematological AEs because of inadequate documentation in case records. Low grade AEs are less likely to be represented, biochemical abnormality or lipid profile testing was not done in asymptomatic patients. Third line TKIs and hematopoietic stem-cell transplantation could not be provided for the eligible cases due to financial constraints.

CONCLUSION

Nilotinib is an effective second line treatment for CML of Indian patients. This is one of the few Indian studies available on the use of nilotinib as second line treatment. Although, this is a small study with relatively short follow up, the difference made by nilotinib in progressive disease (despite high dose of imatinib) and its tolerability is worth reporting. Nilotinib was started at a recommended dose of 400 mg twice daily. This analysis shows certain differences in toxicity profile compared to Western data.

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Ethical Statement: Institutional review committee approval was taken. Formal informed consent is not needed as this is retrospective analysis and it is standard of care treatment. However, general informed consent for data collection was used.

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