Experience with the Use of Nilotinib in Indian Patients

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Abstract Important genetic and ethnic factors could affect the toxicity and efficacy of tyrosine kinase inhibitors. Though nilotinib has been available in India since 2010, there is no report on its safety and toxicity from Indian patients with chronic myeloid leukemia. This is an analysis of efficacy and toxicity of nilotinib when used as a *second line drug* after failure or intolerance to imatinib. Thirty-seven patients started nilotinib [median age 46 years, median duration from diagnosis 5 years, 73% in chronic phase at time of switch] between 2010 to 2016. Reason for switch: failure of imatinib in 33 (89%) and intolerance in 4 (11%). Starting dose 600 mg/day. Dose modifications: 15 (40%) patients required initial dose modifications, but subsequently 25 (67%) patients could tolerate 600 mg/day. Nine (24%) patients were able to tolerate 800 mg/day. The commonest grade 3/4 toxicities were thrombocytopenia (n = 9, 24%), hyperbilirubinemia (n = 7, 18%) and leukopenia (n = 3, 8%). Six patients (16%) discontinued nilotinib due to toxicity while 8 (21%) stopped due to lack of efficacy. After a median duration of 14 months among those continuing nilotinib, 54% of patients responded which included 14 patients who achieved CHR and seven who achieved major molecular response. In the first report on use of nilotinib in Indian patients, we observed a higher incidence of liver toxicity

compared to previous reports. This should be seen the context that all these patients received nilotinib as second line therapy.

Keywords Chronic myeloid leukemia · Nilotinib · Second line therapy · India · Toxicity

Introduction

Nilotinib is a potent second generation tyrosine kinase inhibitor (TKI) for patients with chronic myeloid leukemia (CML). In India, imatinib is the preferred first line therapy and nilotinib and dasatinib are used as second line agents [1]. 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 [2]. In fact, a separate trial called ENEST China was conducted to understand the variability of effect with nilotinib in Chinese population with CML [3]. Though nilotinib is available in India since 2010, there are no studies available on its use in Indian patients. We report our preliminary experience with the use of nilotinib.

Methods

The records of patients with CML receiving nilotinib were identified and reviewed. At our centre, nilotinib was used in the second line setting in those with imatinib failure or intolerance. Nilotinib was generally preferred over dasatinib as the second-line agent as it was cheaper, unless there was data to suggest resistance in a given patient. Complete hematologic response (CHR) was defined as per standard criteria [4], and complete cytogenetic response

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(CCR) was defined by the absence of Ph + metaphases by conventional cytogenetics or by a BCR-ABL transcript level of < 1% by quantitative PCR. Major molecular response (MMR) was defined as the ratio of BCR-ABL to ABL less than 0.1% on International Scale [5].

Whenever feasible, imatinib resistance mutation analysis (IRMA) using nested RT-PCR and sequencing was performed before switching to nilotinib. Patients underwent complete blood counts, renal and liver function tests, electrolytes, blood glucose and lipids, serum amylase, electrocardiogram (ECG) and chest X-ray prior to starting nilotinib and periodically thereafter. All patients started nilotinib at 600 mg daily (increased to 800 mg daily if tolerated). A lower dose (than the recommended 800 mg/day) was chosen because the patients were pre-treated and we were unsure about the toxicity profile. For grade 3/4 toxicity nilotinib was withheld and restarted at a lower dose. Nilotinib was discontinued in patients who couldn't tolerate at least 150 mg/day. Patients were followed with clinical examination, blood counts and relevant laboratory investigations (every week in the first 2–4 weeks, then monthly for 2–3 months, and once in 3 months thereafter). Grading of toxicity was performed according to CTCAE 4.03. RT-PCR for *BCR-ABL* was done 6–12 monthly based on patient's response to treatment. The preliminary experience with efficacy and toxicity is reported.

Results

Patient Characteristics

Thirty-seven patients with CML [median 46 years (range 17–69); 20 males (54%)] received nilotinib between January 2010 and June 2016 (Table 1). The median duration from diagnosis of CML and initiation of nilotinib was 5 years (1.1–23.5 years). Nine patients had medical comorbidities like diabetes or hypertension.

Majority of the patients started nilotinib due to failure of imatinib (n = 33, 89%) (Table 2). IRMA data was available for 27/33 patients (Table 2). Of these, fifteen (55%) patients had a mutation. The commonest mutations were G250E (n = 3) and M244 V (n = 2). Others were E255K, Delh361, E281A, F359V, E355G, F359L, E355A, F311L and F317L (one patient each). Four patients started on nilotinib due to intolerance to imatinib (cytopenia n = 2, skin rash n = 2). The patients who had rash due to imatinib had also lost complete haematological response (CHR) at the time of initiation of nilotinib.

Twenty-seven patients (73%) were in chronic phase at the time of initiation of nilotinib, 7 (19%) were in accelerated phase and 3 (8%) in blast crisis. Median white cell

Table 1 Baseline characteristics

Parameter	N (%)
Age, median (range) (years)	46 (17–69)
Male sex	20 (54%)
Duration from diagnosis (years)	5 (1.1–23.5)
Baseline Sokal category (n = 30)	
High	20 (66%)
Intermediate	6 (20%)
Low	4 (14%)
Reason for switch to nilotinib	
Failure of therapy	33 (89%)
Loss of CHR	20 (54)
Non-achievement of CHR	2 (5)
Non-achievement of CCR	4 (11)
Non-achievement of MMR	2 (5)
Loss of CCR	1 (2)
Loss of MMR	1 (1)
Progression to BC	3 (8)
Intolerance to imatinib	4 (11%)
Mutation detected by IRMA (N = 27)	15 (55%)
Disease status at initial diagnosis	
Chronic phase	33 (89%)
AP/BC	4 (11%)
Disease status at start of nilotinib	
Chronic phase	27 (73%)
AP/BC	10 (27%)
Dose of nilotinib (mg/day) ^a	
600	25 (67%)
800	9 (24%)
300	2
400	1
Dose reduction required	15 (40%)

CHR complete hematological response, CCR complete cytogenetic response, MMR major molecular response, AP accelerated phase, BC blast crisis phase, IRMA imatinib resistance mutation analysis

^aNilotinib was started at a dose of 600 mg/day in all patients and attempted escalation to 800 mg/day when tolerated

count at the time of starting treatment with nilotinib was 44,000/mm³ (3100–1,95,000/mm³).

Outcomes with Nilotinib (Fig. 1)

Median duration of exposure to nilotinib among all 37 patients was 10 months (range 1.5–51 months). Twenty-three patients were continuing nilotinib on last follow-up [Median duration 14 months (range 4–34 months)]. Fourteen patients stopped nilotinib [progressive disease (n = 8) and intolerance (n = 6)]. Of the 23 patients who were continuing nilotinib seven had achieved MMR (30%).

Table 2 Outcomes of switching to nilotinib

Reason for switch to nilotinib	Total N (%)	Responded N (%) Result of switching	No response N (%)	Stopped due to toxicity N (%)
Intolerance to imatinib	4 (10.8%)	4 (100%)	0 (0%)	0 (0%)
Loss of CHR	20 (54.1%)	14 (70%)	4 (20%)	2 (10%)
BC	3 (8%)	1 (33%)	2 (66%)	–
Not achieved CHR	2 (5.4%)	0 (0%)	2 (100%)	–
Loss of CCR/MMR	2 (5.4%)	0 (0%)	1 (50%)	1 (50%)
No achievement of CCR/MMR	6 (16%)	1 (17%)	3 (50%)	2 (33%)

Fig. 1 Flowchart showing the patients included for analysis and their outcomes after start of nilotinib

Dose of Nilotinib

After starting at a dose of 300 mg twice daily, fifteen patients (40%) required reduction of the dose at some point during the treatment period. After gradual escalation of dose, 25 (67%) and 9 (24%) patients tolerated 600 and 800 mg/day (400 mg BD) respectively. Three patients continued nilotinib at reduced doses [400 mg/day (n = 1) and 300 mg/day (n = 2)].

Toxicity

The most common grade 3/4 toxicity was thrombocytopenia (n = 9, 24%) while neutropenia (n = 3, 8%) and anaemia (n = 2, 5%) were less common. Seven patients

(18%) had hyperbilirubinemia [grade 3 (n = 6); grade 2 (n = 1)]. Hyperbilirubinemia was predominantly conjugated and was associated with normal liver enzymes except in one patient. In four patients, temporary discontinuation led to complete resolution and nilotinib could be restarted. One patient had nilotinib related pleural effusion which resolved on temporary cessation and later he could be re-challenged successfully. Six patients (16%) permanently discontinued nilotinib due to toxicity [myelosuppression (n = 3), hyperbilirubinemia (n = 3)]. Other toxicities noted were hyperlipidemia in two patients (5.4%) and renal dysfunction in two patients (5.4%). One patient had hypokalemia but none had electrocardiographic abnormalities or cardiovascular events. No symptomatic pancreatic dysfunction was noted though (we had not actively

Table 3 Comparison of grade 3/4 toxicities of nilotinib in different studies

Study	Current report	Hussain [9]	Gurasova [10]	Nicolini [7]	Saglio [8] ^a
Number	37	82	37	1422	556
Anemia	2 (5%)	–	1 (3%)	42 (3.5%)	18 (3%)
Leucopenia	3 (8%)	2 (2.4%)	5 (14%)	35 (2.5%)	60 (10%)
Thrombocytopenia	9 (24%)	8 (10%)	8 (22%)	308 (21%)	61 (11%)
Hyperbilirubinemia	6 (16%)	NA	5 (13%)	59 (4.1%)	31 (5.6%)
Dermatologic	0 (0%)	2 (7%)	12 (32%)	38 (2.7%)	8 (1.4%)
Discontinuation	16%	NA	18%	14.3%	7%

^aIncluding patients on both 300 and 400 mg BD doses of nilotinib

done pancreatic enzyme testing in any of our patients). None of the patients had significant hyperglycemia or worsening of diabetes.

Discussion

This is the first report on the use of nilotinib from India. Significant toxicity (grade 3 or 4) occurred in about half the patients and six (17%) discontinued the drug due of intolerance. Another eight (21%) had discontinued due to lack of efficacy within the short follow-up time of our report. With careful monitoring and escalations, 2/3rd could tolerate 600 mg/day while few could tolerate 800 mg/day of nilotinib.

The side effect profile seen in our study was similar to earlier reports; thrombocytopenia being the commonest problem [6–8]. We noted a relatively higher frequency of grade 3/4 hyperbilirubinemia in our patients (18% compared with 7–9% in studies reported from the West) [6, 7]. Unfortunately, the only other study from South Asia 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 [9]. Interestingly, a report from Russia showed the similar incidence of hyperbilirubinemia [10]. In all our patients, temporary discontinuation led to the full recovery of liver function and nilotinib was successfully re-challenged in slowly escalating doses in all except 3 patients. The other major concern with nilotinib is cardiovascular toxicity—which was not observed within the short follow-up period [11]. Pleural effusion is a very rare adverse event associated with nilotinib, was observed in one patient [12]. The effusion resolved on stopping nilotinib and did not re-appear when we restarted at a lower dose. Common grade 3/4 toxicities in different studies of nilotinib are compared in Table 3.

We noted a striking discontinuation rate of 37% [progressive disease (21%) and intolerable side effects (16%)]. Discontinuation due to adverse events have been reported to occur in 3–15% patients in other reports [6, 7, 13]. Our cohort had patients with advanced disease at the time of

switching with median duration from diagnosis of 5 years. Among patients who were switched because of loss of CHR, 70% could achieve CHR [6]. However, the rate of achievement of cytogenetic or molecular targets is lower compared to other studies [6, 7]. Presently among 23 patients who are on nilotinib, only 7 patients (30%) are in MMR. Longer follow-up may increase MMR rates [10]. Among patients who switched to nilotinib due to imatinib intolerance, activity was good.

Though this is a small study with relatively short follow-up, this is the first data available on the use of nilotinib from Indian patients and represents the first detailed report of adverse events in this population. However, being a retrospective analysis, grade 1 and 2 side effects are less likely to be represented. Also we started nilotinib at a dose of 300 mg BD initially due to toxicity concerns though the recommended dose in 400 mg BD. Despite these limitations, this analysis shows certain differences in toxicity profile (compared to Western data) especially an increase in hepatotoxicity (when used as a second line agent). This report also highlights the challenges in delivering the usual recommended doses of nilotinib in real-world setting.

Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional/national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent This is a retrospective study and all patients received standard treatment. For this type of study formal consent is not required as per our ethical committee policy.

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