Original Article

Tolerability and Toxicity of Nilotinib in Imatinib Resistent or Intolerant Chronic Myeloid Leukemia in Pakistani Population

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Objective: To monitor the tolerability and toxicity of nilotinib therapy in imatinib resistant or intolerant CML patients.

Study Design: Descriptive case series study

Place and Duration of the Study: The study was conducted at Shaukat Khanum Memorial Cancer Hospital and research Center (SKMCH&RC) Lahore, from December 2009 to June 2011.

Materials and Methods: All eligible patients were monitored by history & physical examination, electrocardiography (ECG), hematologic, electrolytes & pancreatic enzymes evaluation at baseline, after 2, 5, 9 & 13 weeks interval. Data analyzed with SPSS v.19. Toxicity was graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTC v3).

Results: We included 33 eligible patients. Seventy percent (23) were male. Median age 37 years (range 13 – 62). The indications for nilotinib were: Twenty four patients resistant to imatinib and 9 imatinib intolerant. These were generally mild to moderate in intensity. The most frequent adverse effect was myelosupression of which lower grade (1 and 2) thrombocytopenia was commonest (57%). Second most frequent complication was hepatotoxicity. Five patients (15%) had elevation of lipase enzyme out of them 2 had grade 3/4 derangement. Fatal toxicity occurred in only one patient who developed accelerated hypertension, led to massive intracranial hemorrhage and death. None of the patients in our study had serious QT interval prolongation. Treatment was interrupted in eight patients (5 due to hematologic toxicity, one due to hepatotoxicity, one due to elevated lipase and one patient with intracranial hemorrhage).

Conclusion: Nilotinib is generally a well tolerated drug with hematological toxicity being the most common treatment related adverse effect. However due to serious events like intracranial hemorrhage as in our patient and risk of sudden cardiac death, it needs frequent monitoring during treatment.

Key words: Chronic myeloid leukemia, Nilotinib, imatinib resistant, Imatinib intolerant.

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Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder associated with the Philadelphia (Ph) chromosome [t (9; 22) (q34; q11)] resulting in the formation of unique gene product called breakpoint cluster region-Abelson murine leukemia (bcr-abl) fusion gene, which is constitutively an active tyrosine kinase. This deregulated tyrosine kinase is implicated in the development of CML.

Imatinib mesylate [a tyrosine kinase inhibitor (TKI)] is approved for frontline therapy for CML since a decade. It is the drug which led oncology research towards targeted agents. It has been seen that significant number of patients develop resistance to the imatinib.[1] Nilotinib (a 2nd generation TKI) provides immediate hope for patients in whom CML cells have developed resistance to imatinib. However, questions regarding the appropriate or optimal dose, follow-up guidelines, long-term safety and even patient selection remain

open. Furthermore, it remains undefined whether and what comorbidity must be regarded as relative or absolute contraindication for nilotinib.[2]

Nilotinib (AMN107) is a potent alternate Abl inhibitor with activity against many imatinib mesylate-resistant BCR-ABL kinase domain (KD) mutants, except T315I. It is more potent than Imatinib (20-50 times more potent in imatinib resistant cell lines and 3-7 times more potent in imatinib sensitive cell lines) with favorable safety profile.[3] There is no long term survival data yet reported in association with nilotinib for treatment of chronic myeloid Leukemia (CML). Few uncontrolled trials have evaluated the effectiveness of nilotinib in imatinib resistant or intolerant patients. Nilotinib results in complete hematologic response (CHR), major cytogenetic response (MCyR) and complete cytogenetic response (CCyR) rates of 94, 59 and 30 to 40 percent respectively.[4, 5] Nilotinib is an inhibitor of BCR-ABL, c-kit, and platelet derived growth factor receptor (PDGFR). It is able to inhibit both the active and inactive tyrosine kinase configurations.[6] Some of the reported adverse effects of nilotinib which need close monitoring include; myelosupression, QT interval prolongation, sudden cardiac death (0.6%), liver function derangements, elevation of pancreatic enzymes.[7] The optimal duration of therapy, long-term benefits, and toxicity of this newer agent are still under investigation.

Materials and Methods

The present study was carried out at Shaukat Khanum Memorial cancer Hospital and research center Lahore. We inducted patients of more than 12 years of age, confirmed as resistant or intolerant to Imatinib therapy, who were in either chronic or accelerated phase CML. Those who declined Nilotinib treatment, were found allergic to Nilotinib, had abnormal hepatic, renal or cardiac functions or were in blast crisis were excluded from the study. The study was approved by institutional review board. Written informed consent was taken according to institutional guidelines. All patients were treated with nilotinib 400mg twice daily orally. All were monitored by history & physical examination, electrocardiography (ECG), hematologic, electrolytes & pancreatic enzymes evaluation at baseline, then after 2, 5, 9 & 13 weeks interval. Toxic effects were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0. Therapy was interrupted if any patient had grade 3 or more toxicity. All the frequency testing data was analyzed through SPSS v.19.

Operational definitions: Used were as per World Health Organization (WHO) criteria.

Chronic Phase:[8-9] Bone marrow consistent with chronic phase, none of the features of accelerated or blast phase present.

Accelerated phase:[8-9] Presence of one or more of the following features;

- 10 to 19 percent blasts in the peripheral blood or bone marrow.
- Peripheral blood basophils ≥ 20 percent.
- Platelets <100,000/microL, unrelated to therapy.
- Platelets >1,000,000/microL, unresponsive to therapy.
- Progressive splenomegaly and increasing white cell count, unresponsive to therapy.
- Cytogenetic evolution (defined as the development of chromosomal abnormalities in addition to the Philadelphia chromosome).
- **Blast phase:**[8-9] Presence of one or more of the following features;
- ≥ 20 percent peripheral blood or bone marrow blasts.
- Large foci or clusters of blasts on the bone marrow biopsy.
- Presence of extramedullary blastic infiltrates (e.g. myeloid sarcoma also known as granulocytic sarcoma or chloroma).

Intolerance: When Hematological/non-hematological toxicity of at least grade 3 recurs despite appropriate dose reductions and optimal symptomatic management.[8]

Resistance: It is divided into two categories, primary and secondary.

Primary resistance is when a patient fails to achieve a desired response to initial treatment. It includes failure to attain a complete hematologic response after three months of treatment. Failure to attain any cytogenetic response by six months; major cytogenetic response (<35 percent Ph+ cells remaining in the marrow) by 12 months;[10] or complete cytogenetic response (no Ph+ cells) by 18 months.

Secondary resistance occurs when patients with an initial response to imatinib ultimately relapse.[11-14] (Table: I)

Results

Total of 33 eligible patients were enrolled in the study from December 2009 to June 2011. All were treated at Shaukat Khanum Memorial Cancer Hospital and research Center (SKMCH&RC) Lahore, Pakistan. Seventy percent (n=23) were male. Median age was 37 years (range 13 – 62). Twenty four patients were resistant to imatinib and 9 were imatinib intolerant.

Adverse effects were generally mild to moderate in intensity. The most frequent adverse effect was myelosupression. Twenty patients (60%) developed thrombocytopenia, out of them only one had grade 3 toxicity. Twelve patients (36%) developed leukopenia, grade 3 in 3 percent.

Table I: Criteria for definition of "failure" based on European LeukemiaNet recommendations (2006)[27] and criteria for "optimal response" based on European LeukemiaNet recommendations (2009).

	Failure (2006)	Optimal response (2009)
3 months	No hematologic response	CHR, and at least a minor CyR (Ph^+ < 65%)
6 months	Less than CHR No CyR (Ph^+ > 95%)	At least a partial CyR (Ph^+ < 35%)
12 months	Less than partial CyR	CCyR (Ph^+ > 35%)
18 months	Less than CCyR	MMR (3-log reduction in transcripts)
Any time	Loss of CHR, loss of CCyR, kinase domain mutation, insensitive to imatinib	

CHR indicates complete hematologic response; CyR, cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response.

Modified from: Baccarani, M, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 2006; 108:1809.

The criteria are based on the assumption that a patient with chronic myeloid leukemia (CML) in early chronic phase (ECP) starts imatinib at 400 mg daily.
Second most frequent complication was hepatotoxicity. Seven patients (21%) had elevation of bilirubin and three patients had grade 2 elevation of aspartate aminotransferase (AST). Seven patients (21%) had elevation of lipase enzyme out of them 6% had grade 3/4 derangement. Fatal toxicity occurred in one patient who was not a known hypertensive. He developed accelerated hypertension which led to massive intracranial hemorrhage and death (Figure. I).
All patients were closely watched for QT interval prolongation. None of the subjects in our study had serious QT interval prolongation. No one had a QT interval corrected for heart rate (QTc) of more than 480 msec].
Treatment was interrupted in eight (24%) patients: 5 due to hematologic toxicity, one due to hepatotoxicity, one due to elevated lipase and one due to accelerated hypertension leading to massive intracranial hemorrhage and death.

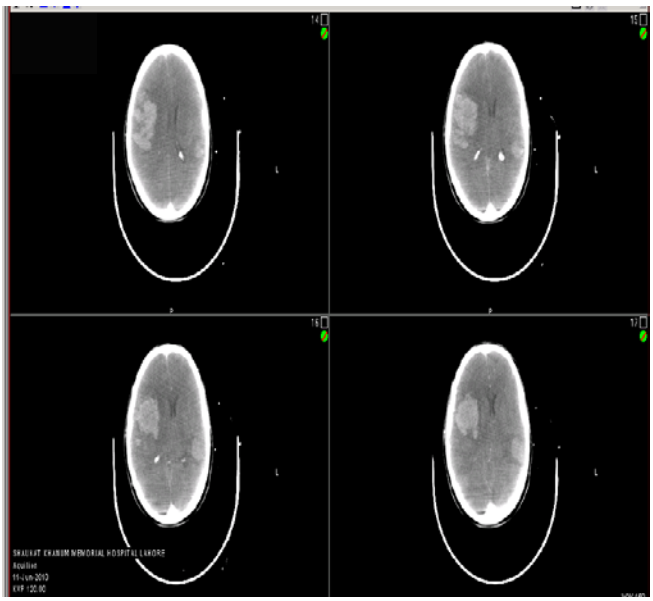

Figure I: Computed tomography (CT) scan of patient, who developed accelerated hypertension, complicated by fatal intracranial bi-hemispheric bleed. Showing mass effects that progressed to trans-tentorial and impending subfalcine herniation.

Discussion

Tyrosine kinase inhibitors have been established as the standard of care for patients with chronic myeloid leukemia. After the success of imatinib therapy, second generation tyrosine kinase inhibitors including nilotinib and dasatinib, which have better potency and selectivity, have appeared in the arena. Nilotinib is now approved for chronic or accelerated phase chronic myeloid leukemia. Earlier studies have shown that there is a degree of difference in pharmaco-genetics in Asian, American and European populations. We investigated the safety and tolerability of nilotinib in a group of Pakistani patients.
Hematologic toxicity including thrombocytopenia 57% and leukopenia 33% was the commonest form of adverse effect seen in our patients. Compared to these figures 49% and 38% thrombocytopenia and leukopenia were reported in ENESTnd trial[15] and by Kantargian H et al[16] 28% and 9% respectively. Interestingly nilotonib causes more thrombocytopenia compared to neutropenia as opposed to imatinib which lowers white cell count more than the platelet count.
Biochemical toxicity in our study included; Hyperbilirubinemia 21%, AST elevation 9% and elevated lipase 15%. While it was reported by ENESTnd trial[15] as 62%, 48% and 29% respectively. Reported by Kantargian H et al [16] as 9%, 6% and 9% respectively and reported by Koren-Michowitz M et al [17] as 17%, 4% and 6% respectively. Other studies (Rosti

G et al and Cortes GE et al) [18, 19] reported it as 39-53%, 29-46% and 29% respectively.

We observed that asymptomatic thrombocytopenia, leukopenia, hepatic and pancreatic enzyme elevation was only of modest degrees. Most of these side effects were manageable by brief interruption of treatment in cases of grade ¾ toxicities. None of the patients developed edema, pleural effusion, pericardial effusion, or pulmonary edema. One of our patients developed fatal accelerated hypertension leading to massive intracranial hemorrhage and death. This was a worrisome event and needs special consideration in future research and management.

Documented literature suggests hemorrhage and fluid retention are much more frequently seen with imatinib than nilotinb, however experience with nilotinib is still limited and needs more time to confirm this observation. Compared to reports in a phase 3 trial, our patients did not develop rash, pruritis or alopecia while receiving nilotinib.Treatment was interrupted in 24% (8) of our patients due to toxicities, while it was interrupted in 66% of patients in a recently published study.[15] Although the limitation of our study was the small number of patients, overall our study confirms that safety profile of nilotinib is comparable with other population groups. Available international studies also contain small population groups therefore it mandates further evaluation in larger groups of patients.

Conclusion

Nilotinib is generally a well tolerated drug with modest degrees of hematological toxicity, which is the most common treatment related adverse effect. However due to serious events like accelerated hypertension leading to fatal intracranial hemorrhage as in our patient and risk of sudden cardiac death. it is imperative that patients receiving nilotinib are frequently monitored during treatment.

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