Original Article

EFFICACY OF NILOTINIB IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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ABSTRACT:

OBJECTIVE: To determine the efficacy of nilotinib in patients of chronic myeloid leukemia, chronic phase, in terms of detection of BCR-ABL by FISH method.
MATERIAL AND METHODS: This study was conducted on 92 diagnosed cases of chronic myeloid leukemia at Department of Oncology, Jinnah Hospital Lahore from August 2016 to January 2017. Patients from either gender, between the ages of 20 to 60 years were included in the study while patients having diabetes and end stage renal disease with glomerular filtration rate less than 15 ml/min were excluded. Nilotinib treatment with the standard dose (300 mg twice daily) was given to patients with chronic phase of chronic myeloid leukemia (CP-CML). Patients were monitored as recommended by the current treatment guidelines. Treatment outcome of CP-CML in terms of efficacy was assessed at the end of 6 months of treatment.
RESULT: The mean age of the patients was 38.84 ± 11.67 years, with male to female ratio of 1.04:1. The mean PH value of the patients was 17.05 ± 18.53 and efficacy was achieved in 36 (39.13%) patients.
CONCLUSION: The efficacy of nilotinib was achieved in significant number of CML patients.
KEYWORDS: FISH, BCR-ABL, Efficacy, Nilotinib, Chronic Myeloid Leukemia.

INTRODUCTION:

Chronic myeloid leukemia (CML) defined as monoclonal myeloproliferative hematological disorder, because of the neoplastic change of the crude hematopoietic undifferentiated cells. These juvenile myeloid antecedent cells isolate and involve the bone marrow and spleen[1,2]. CML occurs because of development and advancement in an irregular clone of cells containing a chromosome revamp known as the Philadelphia chromosome[2,3].
In the Philadelphia chromosome, a piece of the BCR ('breakpoint cluster region') quality from chromosome is melded with the ABL ('Abelson leukemia infection') quality on chromosome[9]. The oncogenic BCR-ABL combination quality encodes the BCR-ABL combination protein. As a protein kinase it leads to myeloid cells uncontrolled proliferation[3,4].
The introduction of Tyrosine kinase inhibitors (TKIs) to control malignant growth has opened new horizons in this field[5]. Imatinib is used as first line treatment in perpetual stage of Ph+CML (CP-CML) and it has brought about high remission and survival rates[3,6,7]. Introduction of second era TKIs, particularly nilotinib, appeared to be more compelling than imatinib as first line treatment in accomplishing critical endpoints as a complete cytogenetic response (CCyR), i.e. the nonattendance of Ph+ cells in blood and bone marrow and a Noteworthy major molecular response (MMR), i.e. the close nonappearance of BCR-ABL combination mRNA transcripts (a decrease to

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≤0.1% on the worldwide scale). By and large, a MMR is accomplished somewhere around one year sooner with the second era TKIs in contrast to imatinib[8,9]. Therapy with nilotinib at dosages of 300 or 400mg BD brought about higher rate of CCyR and a higher rate of MMR following a year than with Imatinib at 400mg (80% versus 65% cytogenetic response rates respectively). The ideal response was BCR-ABL <0.1% following a year of treatment. A local study conducted on imatinib in all phases of CML demonstrated CCyR and complete hematological response tantamount to western populace on imatinib in all phases of CML demonstrated CCyR and complete hematological response Tantamount to western populace on imatinib with major cytogenetic response (Ph<35%). The response in chronic, accelerated and blast phases were 61%, 57% and 28% separately and CCyRs 39.4%, 35.7% and 14.3% individually[10].

METHODOLOGY:

This cross sectional study was conducted on 92 diagnosed cases of chronic myeloid leukemia at Department of Oncology Jinnah Hospital Lahore from August 2016 to January 2017. The patients aged 20-60 years and of either gender with chronic myeloid leukemia diagnosed by bone marrow criteria and nearness of BCR-ABL>1 and Ph>1 by FISH test were included. Patients having diabetes and end organ kidney disease with glomerular filtration rate of <15 ml/min were excluded. Nilotinib treatment with the standard dosage (300 mg twice per day) was given to patients with chronic phase of chronic myeloid leukemia (CP-CML). Patients were followed according to recent treatment guidelines. Result of treatment of Chronic Phase CML patients as far as viability was surveyed at end of a half year treatment.

RESULTS:

The mean age of the patients was 38.8±11.7 years. There were 47(51.1%) male and 45 (48.9%) female patients. The male to female ratio was 1.04:1. Finish sub-atomic reaction (CMR) was accomplished in 36 (39.1%) patients and it was not accomplished in 56 (60.9%) patients. The results of this study demonstrated that 17 male and 19 female patients accomplished finish sub-atomic reaction (CMR). It is Statistically significant with p-value=0.011 (table-I). The results showed that 23 patients (≤ 40 years of age) accomplished finish atomic reaction (CMR), likewise 13 patients (>40 years of age) accomplished finish sub-atomic reaction (CMR), which is statistically insignificant with p-value = 0.191 (table-II).

Table-I: Comparison of patients by efficacy (n=92).

Gender	Efficacy		Total
	Yes	No	
Male	17	30	47
Female	19	26	45
Total	36	56	92

X^2=10.49 p-value = 0.011

Table-II: Comparison of age with efficacy (n=92).

Age (Years)	Efficacy		Total
	Yes	No	
<40	23	28	51
>40	13	28	41
Total	46	56	92

X^2=8.2 p-value = 0.191

DISCUSSION:

The present investigation on finish atomic reaction in CML-CP through FISH following half year of Nilotinib treatment demonstrated that CMR rates are about 39.1%. This study is different from other studies in respect to its duration, that is 6 months and the essential end point i.e MMR/CCyR and PCR. FISH rather than PCR was used in this study.

Another study carried out at Agha Khan Hospital was similar to this study, however, patients were pretreated with imatinib and the method of appraisal was cytogentic reaction by means of FISH as compared to FISH technique for evaluating BCR-ABL protein in this study. Still the two investigations delineated great response with nilotinib in our populace [11].

A study conducted in China showed MMR of 52% following one year of treatment with nilotinib [12]. In another study, conducted in Turkey, 112 patients were treated with nilotinib and were evaluated for MMR following 1-year treatment. The MMR was 66.1%[13]. The present investigation is unique because CMR was the essential end point variable, additionally study duration was 6 months. This study also delineates great response with nilotinib through MMR, however a subset investigation on this outcomes closer. If present study was extended over a period of one year with MMR as end point measure, it may have shown comparable and better results. The outcome of ENEST 1st study in which one of the end point was MMR at the end of two years, the results showed that MMR at end of 3, 12, 18 and 24 months was 29.7%, 56.3%, 65.8% and 61.2% respectively. While 67.3% and 82.5% achieved complete cytogenetic response at end of 6 and 12 months respectively[14]. In contrast to our study, CMR was not assessed in ENEST 1st study. Taking complete cytogentic response as surrogate for BCR-ABL this investigation is supporting current CMR results which is about 40%.

The GIMEMA trial[15] demonstrated that the MMR at 3 and 12 months was 52% and 85% respectively. Combined CMR was 41%, which is almost equivalent and practically identical to our study i.e. 39.1%.

An investigation by Yun SM et al[16] showed that nilotinib resembles imatinib but, as a result of its better geographical fit with BCR-ABL, it is 20 times more potent than imatinib. An examination by Cortes J et al[17] portrayed that TKI treatment with imatinib, nilotinib, or dasatinib results in high response rates, huge numbers of which must be estimated at complete molecular remission.

In this study, complete molecular response (CMR) with nilotinib was accomplished in 39.1% patients of CML, chronic phase, as far as location of BCR-ABL by FISH strategy. Utilization of FISH for BCR-ABL is noteworthy if PCR isn't accessible as the outcomes are in concordance with different investigations. The outcomes were comparable with past referred studies.

CONCLUSION:

Complete molecular response by FISH can be utilized as surrogate for finish complete molecular response by PCR, if patients are non affording.

CONFLICT OF INTEREST:

There is no declared conflict of interest.

ETHICAL REVIEW COMMITTEE:

Ethical review committee of the said institute has reviewed and approved this article.

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Submitted for publication: 08.04.2019

Accepted for publication: 20.04.2019
After Revision