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ORIGINAL ARTICLE

Comparison of Efficacy and Safety of First-Line Drugs (Imatinib Vs Nilotinib) in Newly Diagnosed Patients of Chronic Myeloid Leukemia

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ABSTRACT

Background: Tyrosine kinase inhibitors (TKI's) revolutionized the treatment of chronic myeloid leukemia (CML).
Aim: To compare the efficacy and safety between two Tyrosine Kinase Inhibitors among Pakistani population.
Study Design: Randomized control trial.
Methodology: Patients (n=124) were enrolled through simple random sampling. Prognostic scores were calculated for each patient. The institutional ethics committee of HFH approved this study protocol. Written informed consent was taken. Patients were randomly assigned to nilotinib 600 mg or imatinib 400 mg. The first analysis was done at 12 months of treatment. The second analysis was conducted after patients completed 24 months of therapy with TKIs. A consent form was signed by the participant before taking data. The basic end point was the rate of complete cytogenetic response (CCyR; 0% Ph+ metaphases by cytogenetics) at 12 months. Data was evaluated by using SPSS version 23. Chi-square test was applied with p-value of less than 0.05 was considered significant.
Results: Nilotinib proved superior over imatinib in achieving complete cytogenetic response (94% vs 79%) with significant p-value. Both drugs showed similar risk profile to those from other international studies.
Conclusion: It was concluded that Nilotinib proved clear benefit over imatinib in achieving higher rates of cytogenetic response in our study. The risk of events was comparable with imatinib and nilotinib; but each one showed different kinds of adverse events.
Keywords: Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitors and Cytogenetic Response.

INTRODUCTION

Chronic myeloid leukemia (CML) is categorized as a myeloproliferative neoplasm (MPN) by WHO classification of hematopoietic tumors 2016. CML occurs with a worldwide incidence of 0.0002%[1]. It represents 20% of all leukemias in adults worldwide[2]. It is a clonal disorder which is characterized by genetic translocation i.e., the fusion of ABL1 (Abelson gene) to a BCR (breakpoint cluster region gene) This chromosomal fusion t (9;22) is called Philadelphia chromosome. This causes increased tyrosine kinase activity which is why the discovery of tyrosine kinase inhibitors (TKI's) revolutionized the treatment of CML[3,4].

Currently two TKI's namely Imatinib (trade name Gleevec) and Nilotinib (tradename Tasigna) are available in Pakistan for treatment of Ph-positive chronic myeloid leukemia.[5] Despite the proven efficacy of imatinib, approximately 20% of cases do not show a complete cytogenetic response while others may have side effects or drug resistance[6]. Second generation TKIs i.e., dasatinib or nilotinib result in cytogenetic response in larger proportion of patients and lesser events compared to first generation TKI's[7].

Leukemias are generally classified into two categories i.e., acute leukemias and chronic leukemias[8]. The acute leukemias are then further classified into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). Chronic leukemias are further subclassified into chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML)[9].

The aim of this study was to compare the efficacy and safety of nilotinib vs imatinib as first line treatment in chronic phase CML. There was paucity of data from developing countries on the safety of TKIs in CML. There are no CML treatment registries available in Pakistan. Additionally, data compilation and follow-up in the hospitals is very crude. Till date there have been no published randomized trials of imatinib and nilotinib in Pakistan.

METHODOLOGY

It was a randomized control trial conducted after ethical approval. Patients (n=124) were enrolled through simple random sampling. A detailed history and physical examination were done for each patient. Relevant laboratory investigations (complete blood picture and bone marrow biopsies) were done. Prognostic scores were calculated for each patient. The institutional ethics committee of HFH approved this study protocol. Written informed consent was taken. Patients were randomly assigned to nilotinib 600 mg or imatinib 400 mg. The first analysis was done at 12 months of treatment. The second analysis was conducted after patients completed 24 months of therapy with TKIs. A consent form was signed by the participant before taking data. The basic end point was the rate of complete cytogenetic response (CCyR; 0% Ph+ metaphases by cytogenetics) at 12 months. Further endpoints included rate of CCyR at 24 and 36 months. We also determined the ratio of events in both groups. Patients above 20years of age having positive philadelphia chromosome while no anti-proliferative treatment taken more than two weeks were included. Pregnant patients with Philadelphia chromosome negative CML or lactating mothers were excluded.

Statistical analysis: Data will be entered and analyzed in SPSS version 23.0. At descriptive analysis, for categorical variables, frequency and percentages were figured like age, gender, anorexia, weight loss, weakness, pallor, bleeding, splenomegaly, hepatomegaly, lymphadenopathy, anemia, WBCs, platelets and type of malignancy. Mean and standard deviation were calculated for continuous variables of age, hemoglobin, WBCs and platelets. At Univariable analysis, safety and efficacy were compared with Types of Therapy (Nilotinib and Imatinib) by using chi-square test. P-value 0.05 was considered significant.

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RESULTS

The frequency of male was more than half (n=73) than female 51(41%) with average Spleen size of 5.8cm. There were 117(94.4%) patients of Anemia with average haemoglobin of 9.6 g/dl. The average TLC, %Basophils, %Eosinophils, %Blasts and Platelet count of patients were 226 x 10^9/L, 4%, 3%, 3% and 309 x 10^9/L respectively. However, most of the patients achieved HR 121(98%) and CCyR 102(82%) as shown in Table-1. There was a significant association of Nilotinib and Imatinib with Cytogenetic

response. Patients with Nilotinib (94%) showed significantly higher cytogenetic response as compare to Imatinib (79%) as shown by table-2.

Table 2: Comparison of Efficacy of Nilotinib Vs. Imatinib in CML patients

	n	%age
Age (years)†	43±13.5	
20-30 years	22	18
31-40 years	38	31
41-50 years	31	25
51-60 years	18	14.5
61-70+ years	15	12.1
Gender		
Male	73	59
Female	51	41.1
Anemia		
Yes	117	94.4
No	7	6
Sokal Score†	**0.8±0.2**	
Low Risk	63	51
Intermediate Risk	58	47
High Risk	3	2.4
Hasford Score†	**685±368**	
Low Risk	77	62.1
Intermediate Risk	47	38
High Risk	0	0
HR		
No	3	2.4
Yes	121	98
CCyR		
No	22	18
Yes	102	82
Event		
Yes	61	49.2
No	63	51

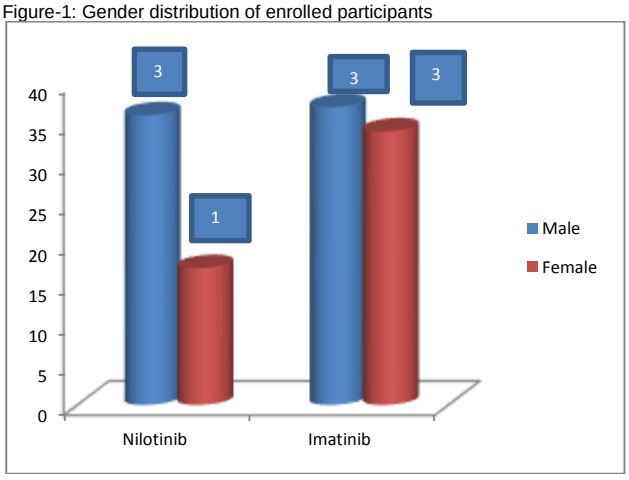
Note: †mean ±SD, TLC=total leukocytes counts, HR= haematological Response, CR= Cytogenetic Response.

Table 1: Descriptive Analysis of Clinico-morphological characteristics of CML Patients

Parameters	Categories	Nilotinib (Tasigna)	Imatinib (Glivec)	P-value
HR	Yes	52 (98)	69 (97)	0.74
	No	1 (2)	2 (3)	
CR in 12months	Yes	50 (94)	56 (79)	**0.01***
	No	3(6)	15(21)	
CR in 24 months	Yes	31 (58.5)	45 (63)	0.58
	No	22(42.5)	26(37)	
CR in 36 months	Yes	27(51)	36(51)	0.97
	No	26(49)	35(49)	

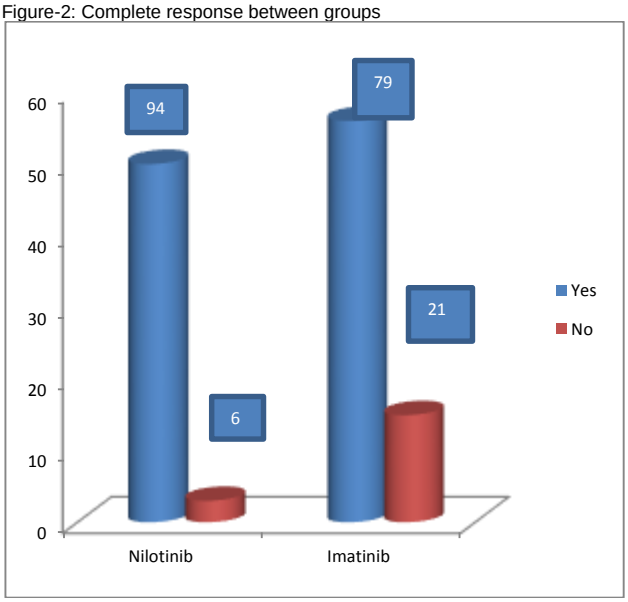
Note: HR= Haematological Response, CCyR= Cytogenetic Response.

Figure-1: Gender distribution of enrolled participants



Gender distribution between both groups was shown in figure-1. Male gender being the dominant one in both groups. Complete response at 12 months of treatment between groups showed significant difference with p-value of 0.001* in figure-2. Better and more response was noticed in both groups.

Figure-2: Complete response between groups



There was no significant association of Events and Reason of Events with Imatinib or Nilotinib in patients as shown in table-3.

Table-3: Comparison of Safety of Nilotinib Vs. Imatinib in CML patients

	Nilotinib (Tasigna)	Imatinib (Glivec)	P value
Event			
Event	26 (49)	35 (49)	
No Event	27 (51)	36 (51)	0.97
Reason			
Progression to accelerated phase	3 (6)	3 (4.2)	
Death	5 (9.4)	7 (10)	
Loss of HR	5 (9.4)	8 (11.3)	
Loss of CCyR	6(11.3)	13(18.3)	
Discontinuation due to toxicity	2 (4)	1 (1.4)	
Loss to follow up	5 (9.4)	3 (4.2)	
No event	27 (51)	36 (51)	0.78

DISCUSSION

The results from our study confirm the superior efficacy of nilotinib as first-line treatment in CML patients as demonstrated by international studies like ENESTnd and ENESTChina.[7-11] Local trials focusing on Pakistani patients are an important step because of the genetic and ethnic differences among populations. With this 3 year of comprehensive follow-up, the nilotinib and imatinib can be easily compared for their benefits as well as risks in CML.

The mean age at diagnosis was 43 years with most of the patients in low and intermediate Sokal and Hasford scores. This is in consistence with the results from ENESTchina (median age 41 years) where patients were younger (median age 46years) and had lower prognostic scores[12-14]. This maybe because CML occurs at a higher proportion in Asians in younger age group than in other populations.[3] Since these calculations take patient age into account, the Sokal and Hasford risk score distribution may be explained by the younger age of patients in our study.

It has been emphasized that cytogenetic response to TKIs is the most significant factor for predicting end result in CML.[12-13] In

the IRIS study patients who achieved a complete cytogenetic response had improved survival. Also, patients who do not show complete cytogenetic response at 12 months have a higher risk of progression to blast crisis.

This study of CML-CP patients has confirmed that nilotinib is highly efficacious as it resulted in early CCy. Additionally, this study collaborated the fact that achievement of CCyR correlates with outcome in CML-CP, regardless of the drug used[12].

ENESTnd also showed that nilotinib resulted in a higher rate of early CCyR i.e , > 95% of cases showed CCyR after 6 months of treatment[7-11]. Our results compare favorably with ENEST and other international studies[7-9].

However, this superior response seen with nilotinib is not seen after 3 years. At 36 months both drugs show cytogenetic response in similar number of patients (51%). This loss of response might be attributed to a number of reasons like: -

1. Selection or evolution of resistant clones
2. Undiagnosed or misdiagnosed co-morbid medical disorders that affect treatment response
3. Poor compliance, missed doses (false sense of relief after 2 years of non-eventful treatment?)
4. Adverse effects of dugs

At 36 months a high percentage of patients have experienced an event (49%) with both drugs. The cause for this needs to be further probed into with investigations (like molecular response monitoring and mutation analysis) and better follow-up of patients. Also, it needs to be compared with similar data from other local hospitals treating CML patients.

All treatments used for the treatment of patients with CML have associated side effects. The rates of freedom from progression were similar with both drugs in our study. This is in contrast to ENESTnd, where nilotinib showed superior response than imatinib.[7-9] This is in consistence with results from ENESTChina.[14] Safety data was also similar to these studies.[15-17]

Limitations of study: The limitations included single centre study with limited resources and finance.

CONCLUSIONS

It was concluded that Nilotinib proved clear benefit over imatinib in achieving higher rates of cytogenetic response in our study. The risk of events was comparable with imatinib and nilotinib; but each one showed different kinds of adverse events.

Author's contribution: AR&SD: Overall supervision and Write up and literature review, **HA&NK:** Statistics application, analysis literature review, help in write up, **NH&HMM:** Literature review help in write-up.

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