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Original Article

A systematic study of hematological and molecular response to generic imatinib mesylate therapy in patients of chronic myeloid leukemia

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ABSTRACT

PURPOSE: Chronic myeloid leukemia (CML) is the commonest hematologic malignancy in India. There are not many systematic Indian studies that assess response to generic Imatinib mesylate therapy on a large scale, since most published trials from the West and India are with Gleevec (Novartis).

METHODS: 101 patients of Chronic Myeloid Leukemia in chronic phase (CML-CP) with a minimum follow up period of 2 years, who had presented to a tertiary care hospital in Western India between 2007 and Feb 2017, were included in this study. All patients received treatment with generic Imatinib Mesylate therapy. Clinical and laboratory examination done at baseline and on follow-up at 1,3,6,9,12 and 24 months was noted. Molecular monitoring with RQPCR at 3 months, 6 months, 12 months and 24 months for BCR:ABL was done.

RESULTS: The study was carried out in 101 CML patients (78 males and 23 females) with a median age of 38 years (4 – 77) years at the time of diagnosis. Complete hematological response was noted in 63 (62.4%) at 1 month, 94 (93.1%) at 3 months, 95 (94.1%) at 6 months, 97 (96%) at 9 months and 99 (98%) at 12 months. At 12 months, 56 (55.4%) patients achieved Major molecular response (MMR) which was defined as BCRABL: ABL gene levels < 0.1%. At 24 months, 66 (65.34%) patients were in MMR.

CONCLUSIONS: Our study using the Indian generic molecule of Imatinib Mesylate demonstrated comparable hematological and molecular responses as published for the parent molecule, Gleevec (Novartis).

KEYWORDS: CML, Molecular monitoring, Generic, Imatinib, Systematic study, chronic myeloid leukemia

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the primitive hematopoietic stem cell and is characterized by the presence of unique translocation, i.e., BCR/ABL1 known as Philadelphia chromosome.[1] CML in the western world occurs with an annual frequency of about 1-2/100,000 of the population and this incidence seems to be fairly constant in different countries.[2] CML is one of the commonest adult leukemia in Indian population accounting for 30% to 60% of all adult leukemias. 90% of patients present in the chronic phase of CML. 10-20% are asymptomatic, being diagnosed as a result of elevated white blood cell count on routine blood sampling.[3] In March 2003, the results of the landmark IRIS Study (Imatinib Compared With Interferon And Low Dose Cytarabine For Newly Diagnosed Chronic -Phase CML) were

published. This trial was a landmark trial that paved the way for the beginning of the imatinib era, making it the standard of care for CML in Chronic Phase (CML-CP).[4] Treatment-related prognostic factors have emerged as the most important prognostic factors in the era of imatinib therapy.

There is lack of Indian studies done which have assessed both hematological and molecular response to Imatinib mesylate (IM) therapy in a systematic manner. This study is aimed at bridging this gap and also to study the safety of the generic Imatinib mesylate in our population. Moreover most published trials from the West and India are with Gleevec (Imatinib mesylate) Novartis.[4-7] The Primary objectives of the study was : To study the hematological response and molecular response to Indian Generic Imatinib mesylate therapy in Chronic Myeloid Leukemia patients with BCR-ABL gene level monitoring at pre defined time points, presenting to a tertiary care hospital in India and The Secondary objectives were to study role of Sokal score[8] as a predictor of therapeutic response and to study the side effects of Imatinib mesylate therapy.

METHODS

It was a single centre, retrospective observational study which was done over 24 months, from February 2017 to February 2019 at a Tertiary care centre in western India**.** The study population included all patients who were diagnosed with Chronic Myeloid Leukemia in chronic phase at our centre and were following up for treatment**.** Institutional Ethics Committee approval was obtained prior to initiation of the study.

All CML patients who were diagnosed initially at our centre in chronic phase, with Imatinib mesylate as the initial primary treatment and who were on regular follow up were included in the study. Informed consent was obtained from all individual participants included in the study. Pregnant women, Patients who discontinued Imatinib therapy for more than 2 weeks consecutively during the initial three months follow up period and patients who presented with accelerated phase/blast crisis were excluded from the study.

Medical records of patients from last ten years (Jan 2007 to Feb 2017) satisfying the eligibility criteria were used for data collection.

Clinical examination including weight, general physical examination, spleen size, complete blood count, peripheral blood smear examination, Liver Function Test, Renal Function Test, uric acid which was done at baseline was noted and hematological and clinical monitoring done at 1,3,6,9,12 and 24 months was noted. Molecular monitoring done at 3, 6, 12 and 24 months for BCR:ABL by RQ-PCR was noted. RQ-PCR test was done from a standardized NABL and CAP accredited laboratory outside the study centre, which was compliant with good laboratory practices. The assay used, quantified the Major (p210), Minor (p190), and Micro (p230) transcripts. Its internal reference gene was ABL1. It was in accordance with EAC Guidelines, and used an (EU) CE-IVD approved kit with high sensitivity (>MR4.5). Its IS conversion factor was established in accordance with the guidelines of Europe Against Cancer (EAC), and had been calibrated using WHO International Standards for CML. All results of RQPCR were reported on international scale as %. Occurrence of adverse effects during the 24 months follow-up was noted. This was the standard protocol at the study centre for asking the patients to come for follow-ups at these intervals. Hence, this data was available from their medical records.

Hematological and Molecular response were evaluated according to the following defined criteria:

Complete Hematological Response (CHR) –

- Platelet Count < 450 x 109 /L
- WBC Count < 10 x 109/L
- Differential without immature granulocytes and with less than 5% basophils
- Non-Palpable Spleen

Major molecular response (MMR): BCR-ABL ≤ 0.10%; Deep Molecular response (DMR) : BCR-ABL ≤ 0.01% on international scale (IS)

Sokal score – a predictor of response in pre Imatinib era, was calculated using the data in the following equation: {Exp {0.0116(age (in years)-43.4) +0.0345(spleen size (in cm below left costal margin)-7.51) +0.188{(platelets(in 109/L)/700)2 -0.563} +0.0887 (blast%-2.10)}[8]

All patients were put on Imatinib 400 mg once daily therapy upfront as an institutional protocol for CML-CP. The imatinib used was generic Imatinib procured by central government on rate contract basis on a yearly tender by open bidding process. Accordingly each year a different brand of generic Imatinib had an opportunity of being supplied. Patients who did not achieve target bcrabl values at different time points (<10% at 3 months, <1% at 6 months and < 0.1% at 12 months) had their dose of Imatinib increased to 800 mg / day. Patients who did not achieve target bcrabl values after Imatinib dose escalation (< 10% at 6 months, < 1% at 12 months and < 0.1% at 24 months) were offered allogeneic HSCT or switch to 2nd gen TKI based on patient preference. Those who refused both options, were continued on Imatinib therapy, after due counselling.

Statistical Analysis:

Data from the case proforma was entered in a Microsoft excel sheet and analyzed using SPSS version 21 software. Descriptive statistics were assessed and represented as Mean±SD, frequencies and percentages. Quantitative data in the single group at multiple intervals was compared using repeated measures ANOVA followed by post-hoc comparisons using Tukeys test for data with normal distribution or Friedmans test followed by pairwise comparisons using Wilcoxon's signed rank test for data which was not normally distributed. Qualitative data between the groups was compared using Chi square test. The level of significance in the study was <0.05.

RESULTS

Data of 128 CML patients who were diagnosed initially at our centre between 2007 to 2017 was available out of which data of 101 patients met the eligibility criteria and was used in final analysis. The 27 patients excluded from the study included patients who presented in AP / BC (n=12), were pregnant women (05), opted for allogeneic HSCT/2nd gen TKI in the initial 12 months of diagnosis (08), discontinued their imatinib therapy for more than 2 consecutive weeks in the initial 3 months of diagnosis (02). The 101 patients included in the study had a median follow up of 6.3 years. All these patients had a follow up of at least 24 months after starting treatment with Imatinib. The mean age of patients at the time of diagnosis of CML was 41.3 years with youngest patient of age of 4 years and eldest patient of 77 years. The Median of age of the patients at the time of diagnosis of CML was 38 years. In the study, majority of patients i.e. 60.4% belonged to the age group of 18-45 years, followed by 21.8% in the 45-60 years age group, 13.9% above 60 years of age and 4% below 18 years of age. In the study, more than 3/4th i.e. 78 (77.2%) patients were males, while females were 23 (22.8%). More

than half of the patients i.e. 53 (52.5%) were central government employees, followed by 23 (22.8%) patients who were housewives. The age distribution and clinical presentation is shown in Table -1.

The most common presenting complaint in patients was fatigue in 43 (42.6%) patients, followed by fever and abdominal discomfort – each in 34 (33.7%), and weight loss in 25 (24.8%). 14 (13.9%) of patients were asymptomatic and diagnosed with CML during evaluation for leucocytosis which was incidentally detected during annual medical examination. Other presentations included bleeding manifestations (3), cough, priapism, vomiting, throat pain (one each). Commonest findings on general examination was pallor in 70 (69.3%) patients, while Splenomegaly was observed in 84 (83.2%) patients, out of which Massive Splenomegaly, defined clinically (> 8 cm palpable spleen) was noted in 34 (33.7%) patients. Hepatomegaly was noted in 44 (43.6%) patients.

Table-1 : Age Distribution and Clinical presentations

Age Distribution		N=101
	<18 y	4
	18 – 45y	61
	45 – 60y	22
	>60 y	14
Presenting Symptoms		
	Fatigue	43
	Fever	34
	Abdominal discomfort	34
	Weight Loss	25
	Asymptomatic	14
	Others	7
Clinical Findings		
	Splenomegaly	84
	Pallor	70
	Hepatomegaly	44
	Lymphadenopathy	4

For initial diagnostic modality, Only FISH for BCR-ABL was performed in 13.9% of patients and only karyotype for Philadelphia chromosome was done in 22.8%, while only RT-PCR for BCR-ABL was done in 28.7%. Combination of Karyotype + RT-PCR was done in 26.7%, while combination of FISH+RT-PCR was done in 6.9%.

The mean hemoglobin at baseline was 10.2+2 gm% (4-15.2). (Median 10.1) The mean total leukocyte count at baseline was 141963.8+107524.9 cells/mm3 (12800-514160). (Median 115000)**.** The mean platelet count at baseline was 327873.7+202339.8 cells/mm3 (40000-1344000). (Median 281000). Blasts were observed in 72 (71.3%) patients while 29 (28.7%) did not have blasts. 25 (24.8%) had 2% blasts, 14 (13.9%) had 3%

blasts, 13 (12.9%) had 1% blasts, 5 (5%) had 5% blasts, 5 (5%) had 6% blasts, 4 (4%) had 4% blasts and 4 (4%) had 7% blasts. All patients had normal liver function tests at presentation. All but 1 patient had normal renal function tests. One patient showed elevated blood urea nitrogen levels – 61 mg/dl and higher creatinine 1.8 mg/dl. The mean uric acid levels in patients was 6+1.6 mg/dl (1.8-11). The mean LDH levels were 549.6+379.8 IU/l (6.5-2673). The Chest X ray findings were normal in all but 1 patient, who showed cardiomegaly. On abdominal sonography, splenic and hepatic enlargement was observed in 86 (85.1%) patients. According to Sokal score distribution at baseline, low risk (<0.8) was observed in 47 (46.5%), intermediate risk (0.8-1.2) was observed in 48 (47.5%), and high risk (>1.2) was observed in 6 (5.9%) patients.

Response to therapy

On follow-up visits, splenic enlargement was observed in 27 (26.7%) patients at 1 month and 2 (2%) patients at 3 months. At subsequent examinations, splenic enlargement was not observed. On follow-up visits, blasts were noted in 3 (3%) patients at 1 month, while subsequent visits did not demonstrate the presence of blasts on peripheral smear. On follow-up, complete haematological response was noted in 63 (62.4%) at 1 month, and 94 (93.1%) at 3 months.

At 3 months, 75 (74.3%) had BCR-ABL gene levels < 10%, while 26 (25.7%) had more than 10%. At 6 months, 64 (63.36%) had BCR-ABL gene levels < 1%, 29 (28.7%) had between 1-10%, and 8 (7.9%) had more than 10%. At 12 months, 56 (55.4%) had BCR-ABL gene levels < 0.1%, 23 (22.8%) had between 0.1-1%, and 22 (21.8%) had more than 1%. At 24 months, 66 (65.34%) patients had BCR-ABL gene levels < 0.1%. Major molecular response (MMR) defined as BCR-ABL gene expression <0.1% was noted in 9 (8.9%) at 3 months, 32 (31.7%) at 6 months, 56 (55.4%) at 12 months and 66 (65.34%) patients at 24 months.

Deep molecular response defined as BCR-ABL gene expression < 0.01% was noted in 5 (5%) at 3 months, 10 (9.9%) at 6 months, 21 (20.8%) at 12 months and 25 (24.75%) at 24 months.

There was a significant association of Sokal score with MMR achievement at 12 months (Table -2). The number of patients achieving MMR at 12 months was significantly higher in those with low risk Sokal score compared to those with intermediate or high risk Sokal score. (P=0.029).

Table-2

SOKAL Group (n=101)	Number of patients at 3 months IM in		Number of patients at 6 months IM in		Number of patients at 12 months IM in	
	CyCR	MMR	CyCR	MMR	CyCR	MMR
Low (n=47)	13 (28%)	02 (4%)	34 (72%)	17 (36%)	40 (85%)	32 (68%)
Intermed (n=48)	11 (23%)	01 (2%)	24 (50%)	17 (35%)	35 (73%)	22 (46%)
High (n=6)	01(17%)	01(17%)	03(50%)	02(33%)	03(50%)	02(33%)

IM= On Imatinib therapy CyCR= bcrabl IS ratio <1% MMR= bcrabl IS ratio <0.1%

Survival

Over a median follow up of 6.3 years (02 – 12), 04 patients died due to disease progression, and another 09 patients progressed to AP / BC. The overall survival was 96%, and event free survival (EFS) was 87%. All the 13 patients who died or progressed, had not achieved MMR at 12 months of therapy.

Adverse Drug Reactions

Skin changes including any Rash or any Hypo pigmentation, was the most common reported adverse event in 28 (27.7%), followed by myalgia in 12 (11.9%), and swelling of face in 10 (9.9%) patients. At 1 month, 5 patients had developed neutropenia out of which 1 patient had severe neutropenia. At 3 & 6 months, 6 patients had neutropenia with none having severe neutropenia. At 9 months, 6 patients had neutropenia with 1 patient having severe neutropenia. At 12 & 24 months, 2 patients had neutropenia with none having severe neutropenia. At 1 month, 32 patients developed Thrombocytopenia out of which 27 were grade 1 thrombocytopenia. At 3 months, 6 months and 9 months, the frequency of thrombocytopenia continued to be almost similar with vast majority of patients having Grade 1 Thrombocytopenia. At 12 months, the frequency of Thrombocytopenia reduced and 21 patients had thrombocytopenia out of which 16 patients had grade 1 thrombocytopenia and only 1 patient had grade 4 thrombocytopenia. 5 patients died during the study period (2-due to disease progression and 3-unrelated to disease).

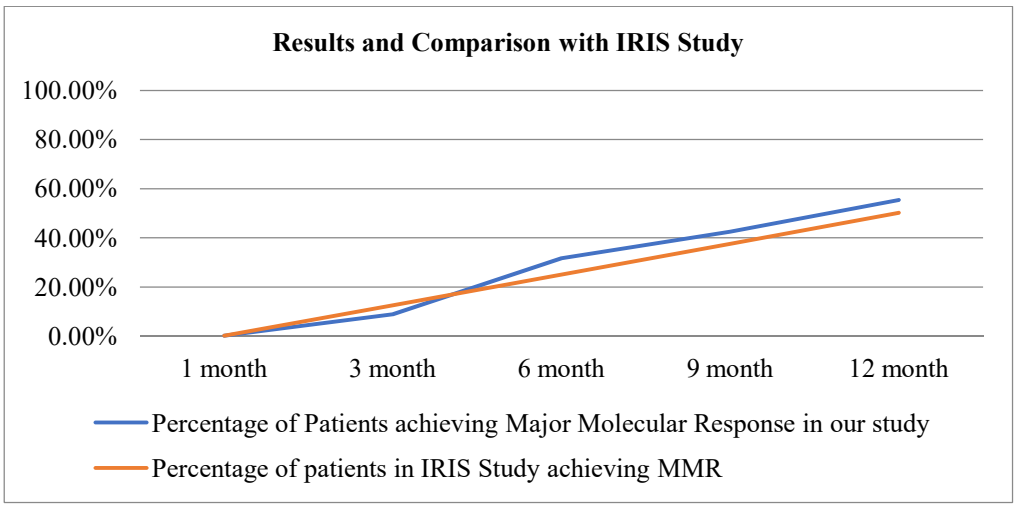
DISCUSSION

The advent of Tyrosine Kinase Inhibitors (Imatinib) has revolutionized the therapy of CML. The goal of therapy in CML now is to achieve a MMR as early as possible so that disease progression to Blast phase is averted.

Our study included 101 consecutive patients diagnosed from 2007 onwards to Feb 2017, as Chronic Myeloid Leukemia in chronic phase and meeting inclusion criteria. All these patients were treated with Indian generic molecule of Imatinib Mesylate as per standard dose. Their hematological and molecular response was noted and studied.

In our study, at 12 months, 56 (55.4%) patients achieved Major molecular response (MMR) which was defined as BCR-ABL:ABL gene levels < 0.1%. In the IRIS and its follow up study by Hocchaus A et al[9] published in March 2017, wherein they had considered major molecular response as patients showing > 3 log reduction in the BCR-ABL:ABL; Major Molecular Remission at 12 months of therapy was seen in 50.2% of patients; which is comparable to our figure. In our study, 66 (65.34%) patients had achieved MMR at 24 months. In a retrospective cohort analysis published in the Lancet in March 2015, data from patients with CML-CP treated in prospective clinical trials with frontline TKI modalities at MD Anderson Cancer Center, Houston, USA, between July 31, 2000, and Sept 10, 2013 was analyzed[10] and in that study, at end of 24 months MMR was noted in 65.51% of patients treated with Imatinib, which is comparable to our figure.

Figure 1: Results and comparison with IRIS study



Adverse events reported in our study: Skin changes including any Rash or any Hypopigmentation, was the most common reported adverse event in 28 (27.7%), followed by myalgia in 12 (11.9%), and swelling of face in 10 (9.9%) patients, while in the IRIS study, the most common side effects were edema and rash.

Strengths of the study: The sample size of 101 CML patients in our study is one of the largest sample sizes among the Indian studies done so far. Our study was done at a large tertiary centre which provides free consultation, laboratory investigations and medicines for its clientele. The clientele are central government employees and their dependents who mostly undergo a yearly health check up. Hence all patients who are diagnosed, are treated and followed up and collection of data was systematic that is – no patients were excluded. The follow up of patients and adherence to treatment and monitoring was done meticulously. Most Indian studies report outcomes of patient who chose to take treatment at that centre, and hence suffer from selection bias. These studies cannot be systematic because of the health care system in our country, where a patient need not follow up in the same medical centre where he / she was diagnosed. Another significant highlight of this study is the fact that in almost all the clinical trials in the West including the IRIS trial and most Indian studies [4-7], the original molecule IM (Gleevec) of Novartis was the drug used in while in our study generic Imatinib mesylate was used to treat all patients.

LIMITATIONS

In our study population, there is a skewed distribution of gender ratio in favour of males is explained by the fact that the study was conducted in a tertiary care centre which primarily caters to central government personnel and their dependents. These central government personnel are mainly young males and they undergo routine annual medical examination including complete blood count and thus many of them are diagnosed as CML at an early stage even before they start showing any symptoms which lead to more patients having low risk sokal score at baseline as compared to other Indian studies.

CONCLUSION

Our study done at a single centre in 101 consecutive patients of CML-CP, all of whom were treated with the Indian generic molecule of Imatinib Mesylate, showed comparable hematological and molecular responses as published for the parent molecule, Gleevec (Novartis). The generic drug was tolerated well and any adverse effects if noted were managed with minimal supportive care. Moreover, its price is nearly one-twelfth of the price of Gleevec, thereby making the Indian generic safe, suitable and cost-effective for Chronic Myeloid Leukemia –Chronic Phase patients in India.

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