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Treatment of chronic myeloid leukemia with Generic Imatinib in patients from Northeastern part of India

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ABSTRACT

Imatinib is now used as the first-line drug to treat CML patient. However, the emergence of resistance to Imatinib in CML patient, the side effect of bone marrow suppression, fluid overload and gastritis are a major limitation of the use of Imatinib in the treatment of CML. This study was conducted to see the therapeutic response and side effect profile of generic Imatinib Mesylate in newly diagnosed CML patients. All cases of CML were given generic Imatinib and followed prospectively with a minimum follow-up of 6 months. They were followed at an interval of 2 weeks till complete hematologic response, thereafter at an interval of 6 to 8 weeks. Cytogenetic and molecular response at the end of one year also evaluated. Among 36 CML patients, 33 were in chronic phase 2 in accelerated phase and 1 in blast crisis while 35 were Philadelphia+ve and 1 was ph–ve at initial presentation. Minimum duration to achieve CHR was 2 weeks with a mean of 5 weeks. At 3 month except one 35 patients achieved CHR (97%). Out of 36 patients, 27 were subjected for Philadelphia chromosome at one year which shown 23 patients (85.18%) achieved a major cytogenetic response. 8 (38%) patients achieved a major molecular response and one patient (4.76%) was having a complete molecular response at one year. 8 (22.22%) patients developed hematological toxicity to Imatinib with Pancytopenia most common. In conclusion, Generic Imatinib is having an excellent therapeutic response in CML patients although higher response rate may be due to smaller sample size and lesser duration of follow up.

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INTRODUCTION

With the FDA approval of Imatinib mesylate, first-generation tyrosine kinase inhibitor in May 2001 average life span of chronic myeloid leukemia patient has increased. Imatinib is now used as the first-line drug to treat CML patient. CML mostly occurs due to reciprocal translocation between chromosome 9 and 22. This translocation results in the head-to-tail fusion of breakpoint cluster region (BCR) gene on chromosome 22q11 with the ABL1 (named after Abelson murine leukemia virus) gene located on the chromosome 9q34, thereby generating BCR-ABL1fusion oncogene. However, the emergence of resistance to Imatinib in CML patient, the side effect of bone marrow suppression, fluid overload and gastritis are a major limitation of the use of Imatinib in the treatment of CML. With the advent of resistance to Imatinib cytogenetic study of Bcr-Abl kinase domain became mandatory for patient not responding to Imatinib. Among different Bcr-Abl

kinase domain mutation, T315I is most prevalent. Patient on Imatinib developing accelerated phase due to Imatinib resistance when shifted to second-generation tyrosine kinase inhibitor as early recognized has shown good long term control of the disease. In all these patient it is important to rule out T315I mutation in Bcr-Abl kinase domain as they will only respond to Ponatinib, if T315i mutation is present, they are left with the option of bone marrow transplant (PDQATE Board-2018).

MATERIALS AND METHODS

Patients who attended hematology OPD at a tertiary care hospital were included in the study. The study was approved by the ethical committee of the institute, and informed consent was obtained from each of the participants. A detailed history and clinical examination of every patient was done. Baseline blood investigation along with Philadelphia chromosome and quantitative BCR-ABL analysis were done at diagnosis. All patients were given Generic Imatinib 400 mg daily. The treatment response was monitored by their complete blood count, spleen size at an interval of 2 weeks till complete hematologic response (CHR) thereafter at an interval of 6 to 8 weeks. The cytogenetic and molecular response were evaluated by using quantitative RT-PCR at the end of one year in affordable patients.

RESULTS AND DISCUSSION

36 newly diagnosed chronic myeloid leukemia patients were included in this study Figure 1.

Among these patients, 33 were in chronic phase 2 in accelerated phase and 1 in blast crisis. 35 patients were Philadelphia positive, and 1 was ph negative at the initial presentation. The median age of presentation was 35 year with SD+14.3 with the minimum, and maximum age of presentation was 9 and 87 years, respectively. Male: Female ratio was 1.8:1. Minimum duration to achieve CHR was 2 weeks with a mean of 5 weeks. At 3 month except one 35 patients achieved CHR (97%) and that one patient diagnosed primary resistance to Imatinib. Out of 36 patients, 27 was repeated for Philadelphia chromosome at one year in which 23 patients (85.18%) achieved major cytogenetic response (McyR). The molecular response was also evaluated in 21 patients at one year by repeating Bcr-Abl transcript level using RT-PCR, which showed 8 (38%) patients achieved major molecular response (MMR) and one patient (4.76%) was having a complete molecular response (CMR) Figure 2.

McyR-Major cytogenetic response (0-35% Ph+ metaphases).MMR-Major molecular response (> 3 log reduction of BCR-ABL from IS or BCR-ABL transcript 0.1% by QPCR). CMR- Complete molecular response (No detectable BCR-ABL by QPCR (IS) using assay with a sensitivity of at least 4.5 logs below IS). CHR- Complete hematological response (Normal CBC and differentials).

Out of 36 patients, 4 were evaluated for BCR-ABL kinase domain mutational analysis as they were either not responding to Imatinib from starting (Primary resistance) or once after achieving CHR went to accelerated/blast crisis (Secondary resistance). Out of four patients, 3 were having BCR-ABL kinase domain mutation, and one patient was negative for BCR-ABL kinase domain mutation, one having T315I, other two were having E459K and H396R, remaining one having mutation other than BCR-ABL kinase domain. Out of 4 patients, one was having primary, and 3 were having secondary resistance. 8 (22.22%) patients developed hematological toxicity to Imatinib. Pancytopenia followed by neutropenia was the most common side effects. One patient on Imatinib developed recurrent Pancytopenia. Out of 8 patients developing cytopenia 2 patient (25%) needed blood product transfusion. Skin hypopigmentation (55.5%) followed by fluid overload and edema (44.4%) were the most common nonhematological toxicity. Decreased sweating was one of the major side effects in patients on Imatinib (30.5%) [Table 1].

Total 5 patients on Imatinib were shifted to other therapy at the end of one year while one patient expired due to blast crisis. One patient who was shifted on Nilotinib developed gynecomastia. Right hemiparesis, along with loss of vision in the right eye was initial presentation in one patient. Splenic infarct with peritoneal hemorrhage occurred in one patient during treatment. Generalized Depigmentation was one of most common side effect in Imatinib group. Painful priapism was present in two patients.

In our study, the median age of presentation was 35 year with male and female ratio (1.8:1). The youngest age of presentation was nine years while the eldest was 87 years old. Patients presenting above 60 year age were 9.3% while below 20 year age was 6%, 32% patient were in the age group of 31 to 40 year. In the western study, the median age of presentation is 53 year *(Harrison's, Eighteenth Edition, Wintrobe's Clinical Hematology, 12th edition*). In most of the Indian study median age of presentation range in between 30 to 40 year (Parikh, 2002; Mishra *et al.*, 1990; Prasad and Singh, 2002; Jabbour *et al.*, 2006; Bansal *et al.*, 2013) . Men are affected more than female in both western and Indian study.

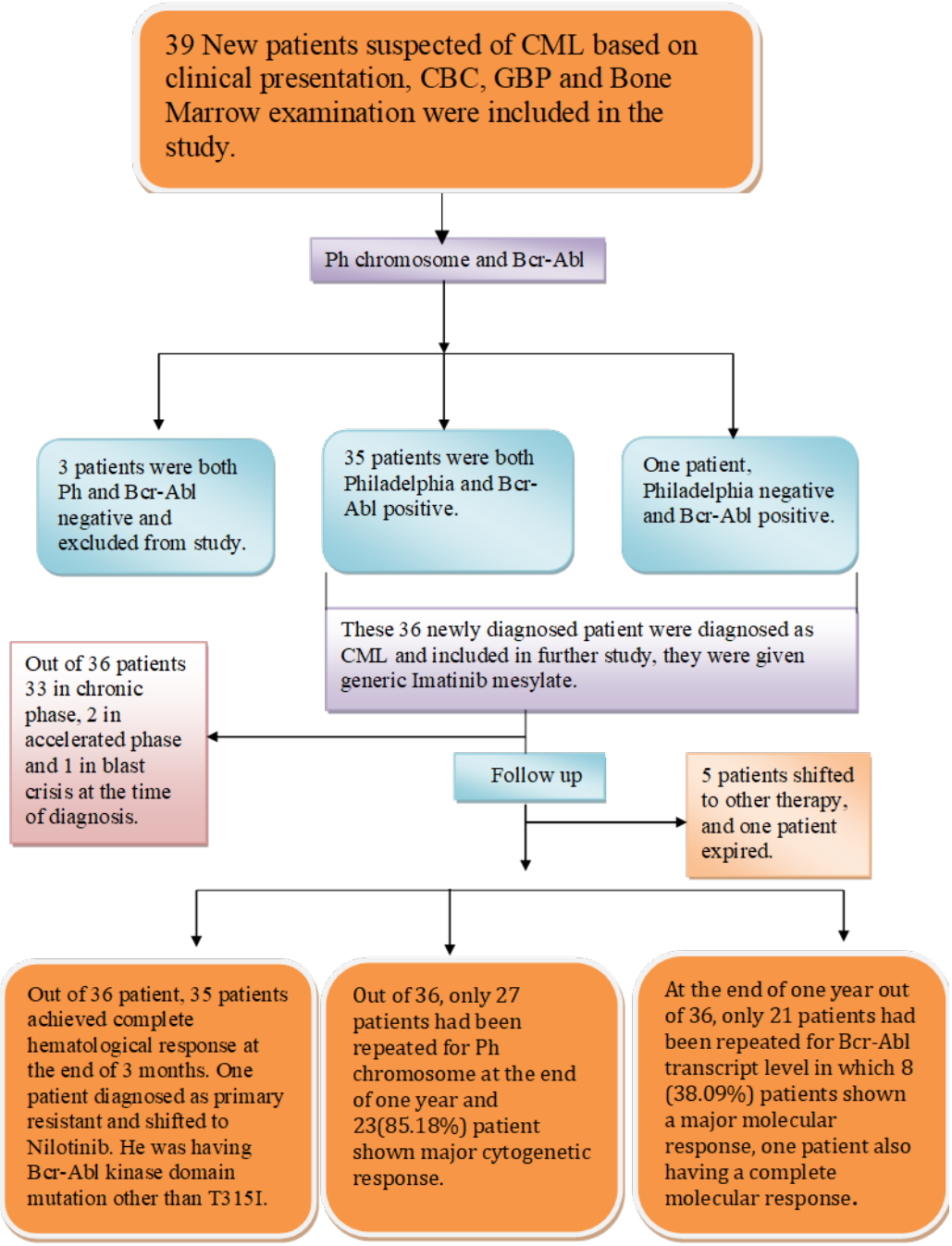

Figure 1: Flow Chart of study

Table 1: Hematological and Non-hematological toxicity of Generic Imatinib

Hematological Toxicity	Patients(N:36)	Non hematological Toxicity	Patients(36)
Megaloblastic anemia	1(2.77%)	Skin Depigmentation	20(55.5%)
Thrombocytopenia	1(2.77%)	Edema/Fluid overload	16(44.4%)
Neutropenia	2(5.55%)	Dyspepsia/Diarrhea	13(36%)
Anemia and Thrombocytopenia	1(2.77%)	Musculoskeletal pain/Fatigue	8(22.2%)
Pancytopenia	3(8.33%)	Hypohydrosis	11(30.5%)
Total	8(22.22%)	Skin rash	2(5.5%)

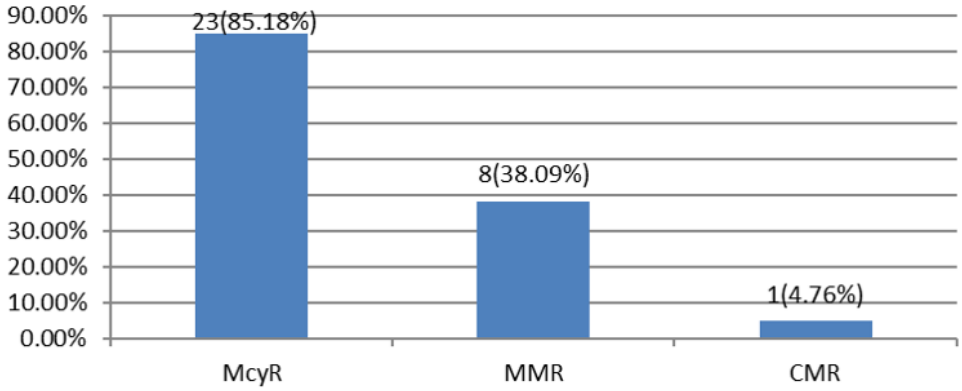

Figure 2: Bar diagram of molecular (N-21) and cytogenetic(N-27) response at end of one year in newly diagnosed patients (n-36) on Imatinib

Table 2: Comparison of non-hematological side effect of Imatinib

Side effect	Jacob *et al.* (2007) (%) 26	Druker *et al.* (2006) (%) 27	Mukhopadhyay *et al.* (2012) (%) 16	Mishra *et al.* (1990) (%) 5	Our study (%)
Skin hypopigmentation	DNA (data not available)	DNA	DNA	30(hyperpigmentation)	55.5
Edema	43	60	70	10	44.4
Dyspepsia/ Diarrhea.	12	45	30	52.5	36
Musculoskeletal pain/Fatigue	15	47	30	50	22.2
Hypohydrosis	DNA	DNA	DNA	10	30.5
Skin rash	35	40	47	15	6

Younger age of presentation in India may be due to average life expectancy is lesser as compared to the western population. Spleen enlargement was presenting complain in 34 (95%) patient. Data from the previous study also show splenomegaly in 95% of CML patient and hepatomegaly in 48% at the time of diagnosis. Mean Bcr-Abl percentage at presentation was 77.38% with SD + 13.06. Its range were in between 37.56 to 100 %. Patient with lower basal Bcr-Abl percentage had a better response to Imatinib and median year of disease-free survival was higher among them. The rate at which a cell develops resistance to Imatinib is determined by its basal level of Bcr-Abl expression. The bcr-abl expression is higher in progenitor cells of patients in blast crisis than in those of chronic phase patients (*Wintrobe's Clinical Hematology, 12th edition*). Less than 10–15% of newly diagnosed patients present with an accelerated disease or with de novo blastic phase CML (Wintrobe *et al.*, 2009; Maru, 2013; Shah, 2013; Deotare *et al.*, 2013).

In our study, 92% patient were in chronic phase, 8% in accelerated phase and blast crisis. Approximately 5% of cases appear to be "Ph-negative" by conventional cytogenetic because of the presence of a cryptic or submicroscopic BCR-ABL rearrangement. These cases require FISH and/or molecular RT-PCR testing for further evaluation and documentation of a BCR-ABL transcript. In the present study, 35 (95%) out of 36 patients were Philadelphia positive, and only one patient was Philadelphia negative. The Minimum duration to achieve complete hematological response was two weeks with a mean duration of 5 Weeks. 35(97%) patient achieved complete hematological response at the end of 3 months of Imatinib therapy. Except one out of 36 patients achieved complete hematological response at the end of 3 months of Imatinib therapy. One patient showed primary Imatinib resistance and shifted to Nilotinib. These data are similar to some other studies conducted in other parts of India (Parikh, 2002; Prasad and Singh, 2002; Doval *et al.*, 2013; Ray *et al.*, 2001). After completing the one year of imatinib therapy karyotyping was repeated in 27 patients, of which 23 (85.18 %) showed major cytogenetic (0 - 35% ph+ metaphase). In *IRIS trial* after a median follow-

up of 19 months, the estimated rate of a major cytogenetic response at 18 months was 87.1 percent in the Imatinib group, and the estimated rates of complete cytogenetic response were 76.2 percent (Deininger *et al.*, 2009). CML data from Kidwai, Bangalore At the end of 6 months, CCR was achieved in 30.13%, and 2.23% patients did not show any CyR, these patients were considered as a failure and underwent Imatinib resistant mutation analysis (IRMA). At the end of 12 months, 66.52% of patients were in CCyR. At the end of 18 months, 78.35% of patients were in CCR Babu (2013). In Deotare *et al.* (2013), CML data from Sterling Hospitals, Gujarat CCyR at 18 months was 55%.11 In this study at the end of one year, 21 patients had been repeated for Bcr-Abl transcript level in which 8 (38.09%) patient shown a major molecular response. One patient was also having a complete molecular response. In Doval *et al.* (2013), 10% of patients had achieved MMR by 6 months, 30% of the patients achieved MMR by 12 months. By 18 months, 55% of patients had achieved MMR, and by 24 months, 67% of patients had achieved MMR. In Mukhopadhyay *et al.* (2012) study Complete Molecular Response was noticed in 70% with a partial response in 19% and poor response almost in 11% at 60 months. The BCR-ABL, T315I mutation causes resistance to Imatinib, Nilotinib, and Dasatinib in chronic myeloid leukemia. Acquired resistance to tyrosine kinase inhibitors (TKIs) in the treatment of chronic myelogenous leukemia (CML) is frequently caused by point mutations in the ABL kinase domain of the BCR-ABL fusion gene. The T315I mutation is the most common mutation found in the kinase domain and leads to complete resistance to existing TKIs. Quantitative level of mutant T315I allele is predictive of major molecular response at 12 months on second-line tyrosine kinase inhibitor nilotinib or dasatinib treatment (Lange *et al.*, 2013). The occurrence of the BCR-ABL1 T315I mutation leads to a very poor therapeutic outcome in chronic myelogenous leukemia (CML) patients treated with tyrosine kinase inhibitors (Alikian *et al.*, 2017). T315I accounts for 4 to 19 % of total Imatinib resistant CML cases (Jabbour *et al.*, 2008; Nicolini *et al.*, 2006; Jabbour *et al.*, 2006). Patients with T315I mutation have a median survival of 12.6 months (Lange *et al.*, 2013; Alikian *et al.*, 2017). Therefore early detection of this mutation could potentially lead to early therapeutic intervention and a better prognosis with the ongoing treatment regimen. Total 4 patients were evaluated for Bcr-Abl kinase domain mutation for various reasons like accelerated/blast phase conversion or no adequate response to Imatinib. Among them 3 were found to have Bcr-Abl kinase domain mutation, one was having T315I, other two were having E459K and H396R, remaining one having mutation other than Bcr-Abl kinase domain. The T315I mutation is the most common mutation found in the kinase domain and leads to complete resistance to existing TKIs. Quantitative level of mutant T315I allele is predictive of major molecular response at 12 months on second-line tyrosine kinase inhibitor nilotinib or dasatinib treatment (Lange *et al.*, 2013) . Among the three patients who were given Nilotinib, one has primary resistance to Imatinib, and the other four have secondary resistance to Imatinib. Approximately 30% of patients with chronic-phase CML on Imatinib experience grade 3–4 Myelosuppression, most commonly Neutropenia, followed by thrombocytopenia. Myelosuppression occurs more commonly in CML patients with accelerated-phase and blast crisis, with rates of 50 to 60% in these patients.3 In our study, the most common hematological side effect was Pancytopenia, total 8(22.22%) patient developed some kind of hematological side effect. Patients developed different kind of cytopenia were confirmed by bone marrow examination to rule out accelerated phase and blast crisis or therapy-related. Out of 8 patients, developed cytopenia, 2 needed blood product transfusion. One patient in Imatinib group developed recurrent pancytopenia, and they were later shifted to hydroxyurea. In Doval *et al.* (2013) 15% patient on Imatinib developed hematological side effect. Neutropenia was the second most common side effect in (Ganesan *et al.*, 2002).

Grade $\frac{3}{4}$ hematological toxicity was seen in 11% of patients (anemia 2%, thrombocytopenia 5.5% and neutropenia 11%). In Mishra *et al.* (1990) Anaemia in 12.5%, Neutropenia in 25% and Thrombocytopenia in 37.5% was seen as hematological toxicity of Imatinib.5 The main side effects noted with Imatinib include fatigue, edema, nausea, diarrhea, muscle cramps, and rash. Cutaneous reactions with Imatinib therapy occur in approximately 15 percent of patients, Hepatotoxicity is uncommon, occurring in approximately 3 percent of patients, usually within 6 months of the onset of Imatinib use (Hensley and Ford, 2003; Sanchez-Gonzalez, 2003; Cross *et al.*, 2006; Singhal *et al.*, 2016). Most common side effect in the present study was skin hypopigmentation (55.5%) while the least common side effect was skin rash (5.5%). The comparative analysis of side effects were described in [Table 2].

Decreased sweating was one of the major side effects in both Imatinib (30.5%) and Hydroxyurea group (20%). None of the patients developed so severe non-hematological side effect that they

needed a change in therapy; whoever patient needed a change in therapy was due to the hematological side effect. Patients developing these side effects were managed symptomatically.

CONCLUSION

Imatinib mesylate has increased the life span of CML patients, and it is now used as a first-line standard drug to treat them. Because of the emergence of resistance to Imatinib these patients require close follow up. If any patient showing suboptimal response or recurrence of initially achieved hematological and molecular response, they need to look for Bcr-Abl kinase domain mutation. Early detection of Imatinib resistance and change of therapy to second-generation tyrosine kinase inhibitor may help the patients who are failing to Imatinib. Myelosuppression may also pose a problem inpatient on Imatinib therapy so close monitoring of hematological parameter like hemogram, general blood picture is required so timely intervention can be done. In our study, higher hematological, cytogenetic and molecular response than other previous studies may be due to smaller sample size and smaller duration of follow up.

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