Imatinib Mesylate Therapy in Patients of Chronic Myeloid Leukemia with Philadelphia Chromosome Positive: An Experience from Eastern India

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Abstract Imatinib inhibits constitutively active BCR-ABL tyrosine kinase of chronic myeloid leukemia (CML). In a long term study it was found superior to interferon alfa plus cytarabine for newly diagnosed CML in the chronic phase. However, till date there is no major study to evaluate eastern Indian CML patients treated with imatinib mesylate. The aim of our study was to see the efficacy, tolerability, toxicity and safety of imatinib in eastern Indian subset of CML population. The present study enrolled 831 patients with CML out of which 197 were excluded due to various reasons of noncompliance, death and not being fit to receive the drug. The rest, 634 (76% of total enrolled) were selected for the evaluation. In the beginning of the study, 603 patients were in chronic phase, 27 in accelerated phase and 4 patients in blast crisis phase. Among 634

patients, 280 patients (44%) received previously either interferon alpha or hydroxyurea and other 354 patients (56%) were previously untreated. Complete hematological remission and major cytogenetic response were 91 and 67%, respectively after 1 year of treatment. Complete molecular remission was 35% after 1 year of treatment. Sixty-four patients (10.1%) were resistant to imatinib mesylate in 5 years. The disease free and overall survival at 60 months were 72.2 and 76.1% respectively. After 60 months of follow up, continuous treatment of chronic phase CML with imatinib as initial therapy was found to be safe and able to induce durable responses in a high proportion of patients.

Keywords Chronic myeloid leukemia · Imatinib · Tyrosin kinase · BCR-ABL transcript

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the expansion of a clone of haematopoietic cells that carries the Philadelphia chromosome (Ph). The Ph chromosome results from a reciprocal translocation between the long arms of chromosome 9 and 22, t(9;22) (q34;q11). The causal association between the Philadelphia chromosome (Ph) and BCR-ABL molecular events and the pathophysiology of chronic myelogenous leukemia (CML) has focused research on strategies that suppress the Ph cells or the expression of BCR-ABL. The molecular consequence of this translocation is a novel fusion gene. BCR-ABL encodes a constitutively active protein, tyrosine kinase [1, 2]. Imatinib mesylate targets the molecular basis of CML by blocking an abnormal tyrosine kinase protein that causes the development of more

granulocytes or blasts than the body needs. Imatinib mesylate, a selective BCR-ABL tyrosine kinase inhibitor, has been reported to demonstrate the remarkable efficacy and tolerability in patients with chronic myelogenous leukemia in chronic phase (CML-CP), either newly diagnosed or after failure of interferon- α treatment [2–5]. The effects of abl kinase activity have been found to be successfully reversed by novel molecule STI571 or imatinib mesylate which specifically binds to the ATP binding site of the BCR-ABL kinases and inhibits them. In the early studies imatinib mesylate has shown promising result in CML in all phases [3, 4, 6]. This drug is an effective treatment for patients with CML in chronic phase as it induces hematological remission in nearly all patients and cytogenetic responses in several patients [2, 5, 7–9]. In a landmark analysis, 90% of patients with a complete haematological response within 12 months has been reported in the earlier studies done in south and western Indian population after starting Imatinib [5, 8]. Before the availability of Imatinib, interferon alfa plus cytarabine were considered standard therapy for patients within the chronic phase of CML [10]. As well as allogenic hematopoietic stem cell transplantation had been the only curative modality for Chronic Myeloid Leukemia. However, it is possible only in a limited number of patients with both acute and chronic graft versus host reactions [5]. Among the nontransplant treatment modalities only interferons produce a cytogenetic response in 15–20% of patients but not without troublesome side effects [5]. After the invention of this molecule it becomes most effective, safe, well tolerable first line therapy in CML [2].

Considering several studies, done world wide, the response rate and toxicity profile of imatinib appear to be different in the different ethnic populations in the world. Imatinib is metabolized in the liver by the cytochrome enzyme system and this enzyme system may be different in different populations as it shows genetic polymorphism resulting in the different pharmacodynamic profile. Several enzyme inducers can induce this enzyme system. Dietary factors, additional non-conventional remedies and alcohol may induce the cytochrome enzyme system and alter the metabolism of imatinib [5].

We have enrolled 831 patients among which 634 patients were recruited for the study during the period of 2002–2010. This is the first retrospective analysis of imatinib mesylate in Eastern Indian population with a large number of patients and our objective was to evaluate the efficacy, toxicity, tolerability and safety of imatinib mesylate in CML patients who were newly diagnosed as well as pretreated with hydroxyurea and or interferon α .

In this study we have reported 60 months of follow up data and the response rates, disease free survival (DFS), overall survival and adverse events of CML patients.

Materials and Methods

Subjects

Total 831 CML patients attended the OPD of Netaji Subash Chandra Bose Cancer Research Institute, Kolkata, India during the period of 2002 to May 2010. The age range was 02–87 years with median age being 36 ± 11.6 years. Among them 86 patients expired and 61 patients discontinued the treatment before starting this study and 50 patients were excluded as they did not fulfill the inclusion criteria of the study. The inclusion criteria were as follows:

- All patients were with Philadelphia (Ph) chromosome positive CML.
- Patients had a life expectancy of at least 12 weeks.
- Patients had an ECOG (Eastern Co-operative Oncology Group) performance status of 0–2.
- Patients signed an informed consent form.

The exclusion criteria were as follows:

- Ph chromosome negative CML patients were not included in this study.
- Pregnant women or nursing mothers were not eligible for this study.
- Patients did not receive any other concurrent chemotherapy or radiation therapy during this study.
- Patients with severe medical problems such as uncontrolled diabetes mellitus, hypertension, severe cardiovascular disease or active infections were not eligible for this study.

The study protocol was reviewed by the ethical committee of the institution. All patients read thoroughly and signed the informed consent, according to the institutional regulation.

So we finally recruited 634 patients (Male = 360, Female = 274) in our study. Average spleen size of patients was 6.6 cm ranging from 2 to 27 cm. A complete data of patient characteristics is given below (Table 1). Previous co-morbidity has been mentioned in Table 2. Treatment was started for newly diagnosed 354 patients within 6 months of the diagnosis. Forty out of 280 pretreated patients received the imatinib therapy within 6 months of diagnosis. Rest of the pretreated patients obtained imatinib therapy after 12 months of the diagnosis.

Study Design

Recommended Doses of Imatinib

As a runtime protocol we have advised imatinib of 400 mg/day as standard dose at chronic phase, 600 mg/day in

Table 1 Shows the profile of studied CML patients

Patient number: $n = 634$, both children and adults were included.

Study period: November 2002 to May 2010

Age range: 02 to 87 years

Median: 36 ± 11.6 years

Sex:

Male: 360 (57%)

Female: 274 (43%)

Previous treatment history:

Untreated: 354

Hydroxyurea: 273

Interferon- α : 7

Phase on diagnosis at the time of presentation:

Chronic phase: 603

Accelerated phase: 27

(20 patients were pre-treated by hydroxyurea and/Interferon- α and low dose cytarabine)

7: Newly diagnosed patients)

Blast crisis: 04

(Pre-treated by hydroxyurea and/Interferon- α and low dose cytarabine)

accelerated phase and 800 mg/day in blast crisis. When the patients in chronic phase showed poor response we gradually increased the dose of imatinib to 600 mg/day and if required 800 mg/day. In case of severe marrow suppression, patients were advised to hold imatinib for 1 week and then again restart after monitoring hematological parameters. Patients were observed very carefully for any adverse effects. Complete hemogram and liver function tests were done once in 2 weeks during the first month and there after monthly. Toxicities encountered were graded as per the National Cancer Institute common toxicity criteria version 2. Hematologic and non-hematologic toxicities were managed with short interruptions of treatment and supportive measures, but the daily dose of imatinib was not reduced below 300 mg/day.

Primary Endpoints and Secondary Endpoints

The primary end point was event free survival which was the actually progression free survival as reported earlier [7]. Events were defined by the first occurrence of any of the incidents like death from any cause during treatment,

progression to the accelerated phase or blast crisis of CML, or loss of a complete hematological and major cytogenetic response. Secondary endpoints were the complete hematological response and complete cytogenetic response in marrow cells. Complete hematological response is defined as a leukocyte count $<10 \times 10^9 \text{ L}^{-1}$, platelet count $<450 \times 10^9 \text{ L}^{-1}$, myelocytes and metamyelocytes $<5\%$, no blast or pro myelocytes, no extramedullary involvement, no signs and symptoms of the disease progression including splenomegaly and blast crisis of CML. Cytogenetic response was defined by counting the Ph positive cells in CML patients. Complete response means no Ph positive metaphase, major response means 1–35% Ph chromosome positive metaphases, minor response means 35–90% Ph chromosome positive metaphases and poor response or no response is considered 91–100% Ph chromosome positive metaphases are obtained. Cytogenetic response is evaluated by analyzing at least 20 cells in metaphase condition of the sample on the basis of G-banding in conventional karyotyping.

The comparative analysis as well as statistical significance levels of hematological parameters like Haemoglobin, total W.B.C count and Platelet count are given in the Tables 6, 7 and 8. The molecular status of the disease has been detected by using standard protocols [11, 12] of FISH (344 patients), RT PCR (90 patients), and FACS (Fluorescence Activated Cell Sorter,) (200 patients). Statistical analysis of all data was done by student t-test and p value denotes significance level. Molecular response was defined as a complete cytogenetic response which was obtained by the use of real-time quantitative polymerase chain reaction to measure the ratio of BCR-ABL transcripts to BCR transcripts. Results were expressed as “log reduction” below a standardized baseline derived from a median ratio of BCR-ABL to BCR obtained from 30 untreated patients with chronic phase CML [7].

Results

Efficacy

The estimated complete hematologic remission was 88% at 60 months. The best observed complete hematologic response (CHR) was 91% at 12 months (Table 3). Best observed complete cytogenetic response (CCR) was 75% at

Table 2 Shows previous co-morbidity associated with many diseases

Disease	Associated tuberculosis	Insulin dependant diabetes	Chronic renal disease	Hypertension with regular medication	Parkinson's disease
No. of patients	15	12	08	50	05

Table 3 Hematological response of CML patients under Imatinib treatment at different time intervals

Months	CHR	Partial	Progression of disease or death
6	570 (89.9%)	38 (6%)	26 (4%)
12	576 (91%)	22 (3.5%)	36 (5.7%)
60	558 (88%)	37 (5.8%)	39 (6%)

CHR Complete hematological response

Table 4 Cytogenetic response of patients under imatinib mesylate treatment at different follow ups

Months	CCR	MCR	Minor	Poor
6	196 (31%)	425 (67%)	38 (6%)	171 (27%)
12	314 (49.5%)	506 (80%)	45 (7%)	83 (13%)
60	475 (75%)	564 (89%)	26 (4%)	44 (7%)

CCR Complete cytogenetic response, MCR Major cytogenetic response

Table 5 Molecular response of the patients who achieved cytogenetic response at different time intervals after imatinib therapy

Months	Complete	Partial	Poor
6	171 (27%)	317 (50%)	146 (23%)
12	222 (35%)	317 (50%)	95 (15%)
60	445 (70.2%)	120 (19%)	69 (10.9%)

60 months (Table 4). The estimated major and minor responses were 89 and 4% with 7% poor response, respectively in 60 months follow up (Table 4). Complete Molecular Response was noticed in 70% with partial response in 19% and poor response almost in 11% at 60 months (Table 5). When molecular analysis was done, we have found that after 1 year, levels of BCR-ABL transcripts had fallen in 35% cases which was 70% ($P < 0.001$) at the long term follow up (5 years) (Table 5).

Long Term Outcomes

Follow up data at 60 months revealed the estimated event free survival (EFS), 72.5% (Table 9) and an overall

survival, 76.1%, respectively (Table 9). Among 634 patients receiving imatinib, 64(10.1%) progressed to the accelerated phase or blast crisis, 19 (3%) had a hematologic relapse. 53 patients (8.4%) (Table 9) died among which 9 unrelated to the disease(septicaemia-4, fatal road accident 2, cerebro vascular accident 3).The estimated annual rate of treatment failure after the start of imatinib therapy was 1.3% in the first year, 3.5% in the second year, 2.2% in the third year, 1.9% in the fourth year, and 1.2% in the fifth year. Imatinib response data have been mentioned below in Tables 3, 4, 5, 6, 7, 8 and 9. Status of the patients at 60 months follow up has been depicted in Table 9. Clinical history of long term survivors showed that almost 86% of EFS patients started their imatinib treatment within 6 months of diagnosis but others started after 6 months of diagnosis.

Adverse Events

After a follow up of 60 months, the adverse events found, were similar to those reported previously but intensity or grade of side effects are quite different in our present study in comparison to others (Table 10) [5, 7, 8]. The most commonly reported adverse events were edema (including peripheral and periorbital edema) (70%), muscle cramps (40%), diarrhoea (30%), nausea (50%), musculoskeletal pain (30%), rash and other skin problems (47%), abdominal pain (37%), fatigue (39%), joint pain (31%), and headache (35%). Grade 3 or 4 adverse events consisted of neutropenia (27%), thrombocytopenia (15%), anemia (10%), elevated liver enzymes (5%), and other drug-related adverse events (15%).

Though, it was a cosmetic problem and did not pose a substantial medical hazard, still an interesting dermatological effect- the generalized hypo-pigmentation was noticed in 75% of our CML patients. Probably, this is due to the side effect of imatinib mesylate. As imatinib is an inhibitor of BCR-ABL tyrosine kinase it inhibits the activity of platelet derived growth factor and C-kit tyrosine kinase proteins, thus interrupt the development and differentiation of melanocytes and produces the hypopigmentation [13].

Table 6 Comparative analysis of different hematological parameters pre treatment and follow up treatment of the patients under Imatinib therapy

Parameters	Pre treatment Mean $\pm$ SE	Post treatment (after 6 months) Mean $\pm$ SE	Post treatment (after 12 months) Mean $\pm$ SE	Normal control Mean $\pm$ SE
Hb% (g/dl)	10.85 $\pm$ 0.35	12.08 $\pm$ 0.46	13.08 $\pm$ 0.57	14.05 $\pm$ 0.13
Total Leukocyte Count ($\times 10^3/\mu\text{l}$)	144.8 $\pm$ 10.6	20.32 $\pm$ 3.39	8.44 $\pm$ 0.56	7.63 $\pm$ 1.40
Platelet Count ($\times 10^3/\mu\text{l}$)	97.32 $\pm$ 6.35	117.7 $\pm$ 5.9	138.6 $\pm$ 6.83	197.1 $\pm$ 9.04

SE Standard error, P value denotes the significance level

Table 7 Shows the significance levels (detected by *P* value) of different hematological parameters of pre & post treatment of CML patients under imatinib therapy

Parameters	Pre treatment versus post treatment (after 6 months)	Pre treatment versus post treatment (after 12 months)
Hb% (g/dl)	$P < 0.025$	$P < 0.005$
Total Leukocyte Count ($\times 10^3/\mu\text{l}$)	$P < 0.0005$	$P < 0.0005$
Platelet Count ($\times 10^3/\mu\text{l}$)	$P < 0.0005$	$P < 0.0005$

Table 8 Shows significance levels of different hematological parameters of normal control and pre & post treatment CML patients who underwent Imatinib therapy

Parameters	Normal versus pre treatment	Normal versus post treatment (after 6 months)	Normal versus post treatment (after 1 year)
Hb% (g/dl)	$P < 0.0005$	$P < 0.05$	$P < 0.025$
Total Leukocyte Count ($\times 10^3/\mu\text{l}$)	$P < 0.0005$	$P < 0.005$	$P < 0.1$
Platelet count ($\times 10^3/\mu\text{l}$)	$P < 0.0005$	$P < 0.005$	Not significant

Table 9 Shows the status of the patients at 60 months follow up

Events	No. of patients
Disease free survival	459 (72.5%)
Overall survival	483 (76.1%)
Discontinued	67 (10.5%) [46 patients could not afford and 21 patients shifted to other places]
Death	53 (8.4%) [9 patients unrelated to the disease and 44 patients due to progression of the disease]
Loss to follow up	30 (4.7%) [Due to socio- economic reason]

Discussion

Imatinib mesylate has brought about a paradigm shift in the management of CML patients [5]. Five years continuous treatment of chronic phase CML with imatinib as initial therapy was found to induce durable responses in a high proportion of patients. Previously a major study by Brian J. Druker et al., 2006 showed the results of treatment of 553 patients with Imatinib [7]. They randomly assigned 553 patients to receive imatinib and 553 to receive interferon alfa plus cytarabine and then evaluated them for overall

and event free survival; progression to accelerated phase CML or blast crisis; hematologic, cytogenetic, and molecular responses; and adverse events. Patients who had a complete cytogenetic response or in whom levels of *BCR-ABL* transcripts had fallen by at least 3 log had a significantly lower risk of disease progression than did patients without a complete cytogenetic response ($P < 0.001$) [7].

Another important study was done at the M.D. Anderson Cancer Centre [2] with 50 patients. Few Indian studies about the imatinib therapy were reported earlier [5, 8, 14] where the number of early chronic phase CML patients were 24 with a median age of 30 years [5], 100 with a median age of 32 years [8] and 400 patients [14]. Our present study evaluated 634 patients with a median age of 36 years. Among them males were slightly frequent than females (ratio 1.3:1) as reported in other studies also [15].

We observed 31% CCR and 67% MCR at 6 months which are compatible with the data of study group of Jacob et al., 2007. But at the end of 12 months, CCR and MCR were reported to be 38 and 55% in this study group (Table 11) [8] which were in higher side in our eastern Indian study group (49.5 and 80%, respectively, Table 4). Though, complete and major cytogenetic responses (CCR and MCR) are observed to be higher in the north Indian study group 53/72% [14] as well as in the western study groups—69/85% [7] and 72/90% [2] in comparison to our present data. Rajappa et al. 2008 from Hyderabad, India showed 56% complete cytogenetic response among 201 CML patients at 29.5 months median follow up [16].

Regarding haematological response, we achieved 91% complete remission at the end of 1 year which is likely to be same, reported by Jacob et al., 2007 and less than the data reported by Deshmukh et al., 2005. CHR is also in higher side in western studies being 96 and 98%, respectively reported earlier by Brian J et al. and Kanter jian HM et al. [2, 7].

In our present study, at 60 months of follow up, the estimated event free survival was 72.5%, and an estimated 76.1% of patients had not progressed to the accelerated phase or blast crisis. The study with a major number of patients (1106 cases) by Brian J et al., 2006 revealed the event free survival of 83% and overall survival of 93% at 60 months follow up which are in the higher side in comparison to our present study. Another Indonesian study [15] reported 66% overall survival at 60 months follow up. Little low overall survival data of Asian population of CML patients may be due to late start of imatinib after the diagnosis but further investigations and molecular research are needed in this regard.

Out of 197 patients (among enrolled 831), who were unfit for inclusion criteria, 156 had already received hydroxyurea and or interferon α . There were no durable

Table 10 Comparative analysis of side effects of imatinib therapy in CML patients among different studies

Adverse effects	Jacob et al. [8] (South Indian study)	Brian J et al. [7] (Western Study) (%)	Present study, 2011 (Eastern Indian Study)
Superficial edema & weight gain	43%	60	70%
Skin rash	35%	40	47%
			Grade I & II: 30%
			Grade III :11%
			Grade IV: 6%
Musculoskeletal pain	15%	47	30%
Gastro intestinal (vomiting, diarrhoea)	12%	45	30%
			Grade I: 18%
			Grade II: 12%
Neutropenia	16%	17	27%
	Grade III: 11%		Grade I & II: 10%
	Grade IV: 0.5%		Grade III: 11%
			Grade IV: 6%
Thrombocytopenia	Grade III: 07%	9	15%
			Grade III: 9%
			Grade IV: 6%

Table 11 Comparative analysis of response of imatinib therapy in CML patients in respect to hematological and cytogenetic responses among different studies

Study	Follow up period (months)	No. of patients	CHR (%)	MCR (%)	CCR (%)
Brian et al. [7]	12	1106	96	85	69
Kantarjian et al. [2]	9	50	98	90	72
Deshmukh et al. [5]	12	24	100	62.5	41.7
Jacob et al. [8]	12	100	90	55	38
Present study, 2011	12	634	91	80	49.5

cytogenetic or hematological responses observed among them. Out of 280 pre-treated patients (among 634 recruited) 24 had progressed to accelerated or blast crisis phase and other 256 had only hematological and minor cytogenetic response. After starting imatinib therapy, 150 patients (53.6%) of this group achieved a haematological and cytogenetic response within 6 months. This data indicated the superiority of imatinib over hydroxyurea and or interferon α and cytarabine.

Comparative analysis of haematological parameters like haemoglobin, total Count, platelet count between patients and normal population reveal that the pre treatment values against normal values are very significant. The post treatment values of the haematological parameters are very close to the normal values and hence it can be proved that the imatinib therapy is effective specially for the CML patients.

Regarding the toxicities, generated by imatinib mesylate therapy, the significant difference has been observed in haematological toxicities. Incidences of neutropenia and thrombocytopenia are comparatively lower in other studies [7, 8]. Among other toxicities superficial edema, weight gain and water retention are quite high in our eastern Indian CML patients but other toxicities are comparable to the previous reports [5, 7, 8]. Sixty-four out of 634 patients (10.1%) in 60 months follow up study showed intolerance with imatinib mesylate. Patients, who are in disease progression or blast crisis, may acquire additional cytogenetic abnormalities. It may induce the conformational change of the BCR-ABL fusion protein further which may not be blocked by the tyrosine kinase inhibitor activities of imatinib mesylate alone. So, further molecular mutation detection are needed for these patients and accordingly new targeted therapy (Nilotinib, Dasatinib, Basutinib etc.) [17] may be planned.

Conclusion

Imatinib mesylate is very effective and safe drug to induce durable response in large population of CML patients. It is observed to be superior to hydroxyurea, interferon α and cytarabine in newly diagnosed CML patients. Based on our study and other similar studies done in Indian and Western countries, we can conclude that imatinib mesylate is the best treatment option as a first line therapy for the CML patients.

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