■ *Original Article*

Safety Profile of Imatinib in Indian Chronic Myeloid Leukemia Patients

R Meena[1], N. R. Biswas[1], Lalit Kumar[1] , T Velpandian[2] and Y K Gupta[3]
[1]Department of Pharmacology, [2]Department of Medical Oncology, [3]Department of Ocular Pharmacology,
All India Institute of Medical Sciences, New Delhi – 110029 , INDIA

Abstract

Introduction: Imatinib mesylate has become the choice of drug in the treatment of chronic myeloid leukemia. **Objective:** To study safety profile of Imatinib (specific inhibitor or bcr-abl tryosne kinase protein) in *Philadelphia* chromosome t {(9:22), bcr-abl} positive chronic myeloid leukemia (CML) chronic phase patients. **Materials and Methods:** After IEC clearance, 36, BCR-ABL positive CML patients in the chronic phase of the disease were recruited. Imatinib mesylate (Gleevec, Novartis), was started (400mg daily) and followed up weekly in first month, two weekly till three months & monthly thereafter. Safety profile data, recorded in pre-designed proforma, were analyzed for time of onset, duration and severity of adverse effects. Causality relationship of recorded adverse events was established with imatinib therapy using WHO-UMC criteria. **Results:** A total of 222 adverse events were reported in 36 CML-CP patients over 12 months of follow up. Thrombocytopenia was the most commonly reported in 60% of the patients followed by musculoskeletal (17%), dermatological (16%), gastrointestinal disturbances (13%), body weight changes (11%), superficial edema (8%) and liver enzyme rise (4%). More than 80% events reported within months of therapy which persisted for less than 3 months in most of the cases. No treatment was needed in 68% of cases while therapy alteration was not needed in 88% of cases. Most of the reactions (60%) had probable relationship with the therapy. **Conclusion:** Imatinib was well tolerated, having only mild to moderate grade of toxicities, mostly within 3 months of therapy and most of them persisted for less than 3 months of duration, requiring only symptomatic treatment and drug withhold or dose decrement in only few cases.

Keywords: Safety profile, imatinib, causality assessment, adverse events.

Introduction

Imatinib mesylate, 2-phenyl amino pyridine, has brought paradigm shift in the treatment of chronic myeloid leukemia (CML) which is clonal stem cell disorder in which cells of the myeloid series undergo massive clonal expansion.[1] CML is caused by tyrosine kinase activity of fusion protein BCR-ABL formed by the reciprocal translocation between the long arm of chromosome 9 and 22.[2l] Imatinib acts by competitively blocking the ATP binding site at BCR-ABL tyrosine kinase, so inhibiting the phosphorylation of tyrosine residue of target protein in the signal transduction pathway, hence excessive cell proliferation occurring in CML is interrupted and apoptosis is induced.[3] Imatinib is metabolized by liver microsomal enzyme system mainly CYP3A4 and CYP3A5.[4] P-Glycoprotein expression in the leukemia cells affect the bioavailability of the drug.[5] Imatinib is well tolerated drug showing adverse events of mild to moderate severity. The most frequently reported adverse events during imatinib therapy are nausea, vomiting, edema, muscle and bone pains, arthralgia, skin rash, diarrhea, fatigue, weight gain, hematological toxicity and hepatotoxicity [6,7]. Severity and frequency of reported adverse events increase with dose[3] and in advanced phases

Address for correspondence:
Prof. N.R. Biswas, Govt. of India Advisor to BPKIHS
& Prof. of Clinical Pharmacology & Therapeutics
B.P. Koirala Institute of Health Sciences, Dharan
Email: nrbiswas@hotmail.com

of CML [6,8,9]. There are inter-individual and racial variations in all of the above mentioned factors affecting safety profile of the drug. Studies[10, 11] in Indian chronic myeloid leukemia patients has shown different safety profile of imatinib from landmark Western studies[6,7]. But data from these preliminary Indian studies are not sufficient for making conclusion. So we planned to record adverse events of imatinib in newly diagnosed Indian chronic myeloid leukemia patients, establish causal relationship of these events with imatinib and compare these results with landmark Western studies and previous Indian studies.

Methodology

Chronic myeloid leukemia (CML) patients coming to the Medical Oncology OPD, Dr. BRAIRCH, AIIMS, New Delhi, between July, 2006 and June, 2007 were enrolled in the study according to following criteria.

Inclusion criteria:- i.) All age groups and both sexes. ii.) Newly diagnosed Philadelphia chromosome or BCR-ABL gene positive CML iii.) Planned for imatinib mesylate therapy for chronic phase CML. ***Exclusion criteria***:- (Patients with i.) Serum bilirubin, ASG or ALT, creatinine level of more than twice of upper limit of normal range. ii). Eastern Cooperative Oncology Group performance status score of e" 3.iii) Grade III/IV cardiac problem as defined by the New York Heart Association criteria iv) on any other anticancer therapy except hydroxyurea (if needed) or the drugs which interact with imatinib (CYP3A4 inhibitors or inducers).

Institutional ethics committee approval was taken and written informed consent was taken from all the patients after explaining the risks and benefits of the study in the languages they understood.

Study design: After taking informed consent and baseline evaluation of each included patient, imatinib mesylate (Gleevec, Novartis - provided free through Gleevec International Patients Assistance Programme or **GIPAP**, Max Foundation, USA) therapy was started as the single oral dose of 400 mg or 250 mg/m^2 per day in chronic phase. Patients were followed up for the maximum duration of 12 months. All adverse events during treatment were recorded in a proforma Toxicities were graded according to Common Toxicity Criteria of National Cancer Institute.[12] Dose adjustment were done during toxicities according to standard guideline.[13] Causality assessment of reported adverse events was done using WHO-UMC system.[14]

Result

Adverse events were reported in 36 chronic phase CML patients on imatinib therapy. A total of 222 adverse events were reported during 12 months of therapy, which were evaluated for time of onset, period of persistence, treatment needed and alteration of therapy are shown in fig 1.and table 2, 3 & 4 respectively.

No treatment of adverse events was needed in 68% of cases. Only symptomatic treatment was needed in about 28% of cases while about 5% required specific therapy .Therapy was not altered for about 88% of adverse events. Drug was withheld only in hematological toxicities, mainly grade II/III thrombocytopenia and grade III neutropenia. Drug withhold followed by permanent dose decrement was needed in case of prolonged thrombocytopenia in about 5 cases.

Commonly Reported Adverse Events (Table 1)

Table 1. Adverse events of imatinib in Indian CML-CP patients (n=36); Total No. of adverse events (AEs) = 222

A. Hematological adverse events

Adverse Events	Grade I/II (In patients)		Grade III/V (In patients)		In total no. of patients(%)	Total (% of total adverse events)
	No.	%	No.	%		
Thrombocytopenia	15	41.7	7	19.4	22 (61)	54 (24.3)
Leucopenia	9	25.0	3	8.3	12 (33.3)	
Neutropenia	10	27.8	3	5.6	12 (33.3)	
Anemia	7	19.4	1	2.8	8 (22.2)	

B. Non-hematological adverse events

Adverse Events	Grade I/II		Grade III/V		Total No. (%)	Total (% of total AEs)
	No.	%	No.	%		
Musculoskeletal						38 (17.1)
Muscle Pain	10	27.8	1	2.8	11 (30.6)	
Muscle cramp	12	33.3	1	2.8	13 (36.1)	
Arthralgia	8	22.2			8 (22.2)	
Fatigue	6	16.7			6 (16.7)	
Dermatological						35 (15.8)
Skin rash	10	27.8	1	2.8	11 (30.6)	
Pruritus/itching	4	11.1			4 (11.1)	
hypo pigmentation	10	27.8			10 (27.8)	
Hyper Pigmentation	4	11.1			4 (11.1)	
Nail bed Pigmentation	3	8.3			3 (8.3)	
Alopecia/Hair fall	3	8.3			3 (8.3)	
GI disturbances						28 (12.6)
Nausea	8	22.2			8 (22.2)	
Vomiting	3	8.3			3 (8.3)	
Dyspepsia	9	25.0			9 (25)	
Diarrhea	2	5.6			2 (5.6)	
Constipation	4	11.1			4 (11.1)	
Abdominal pain	2	5.6			2 (5.6)	
Body weight changes						
Weight gain	18	50.0	4	1.8	22 (61.1)	
Weight loss	2	5.6			2 (5.6)	
Superficial edema						17 (7.7)
Facial puffiness	14	38.9				
Pedal/Ankle	2	5.6	1	2.8	3 (8.3)	
Liver toxicity						9 (4.1)
OT/PT↑	1	2.8			1 (2.8)	
ALP↑	6	16.7			6 (16.7)	
Bilirubin↑	1	2.8			1 (2.8)	
Total Protein↓	1	2.8			1 (2.78)	
Others						17 (7.7)
Headache	5	13.9			5 (13.9)	
Dizziness	1	2.8			1 (2.8)	
Loss of appetite	2	2.8			1 (2.8)	
Blurring of vision	1	2.8			1 (2.8)	
Decreased vision	1	2.8			1 (2.8)	
Pleural effusion	1	2.8			1 (2.8)	
Epistaxis	1	2.8			1 (2.8)	
Gum bleed	1	2.8			1 (2.8)	
Livedo reticularis (legs)	1	2.8			1 (2.8)	
Subcojunctival hemorrhage	1	2.8			1 (2.8)	
Restlessness	1	2.8			1 (2.8)	
Generalized skin edema	1	2.8			1 (2.8)	

Table 2: Onset of adverse events in Indian CML-CP patients (n=36)

Onset of Adverse events	≤ 4 wks		5wk - 3m		Total ≤ 3m		4m - 6m		7m - 12m	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total (222)	**99**	**44.6**	**80**	**36.0**	**179**	**80.6**	**32**	**14.4**	**11**	**5.0**
Musculoskeletal	24	10.8	6	2.7	30	13.5	8	3.6	1	0.5
GI disturbances	21	9.5	5	2.3	26	11.7	1	0.5	1	0.5
Hematological	16	7.2	26	11.7	42	18.9	8	3.6	4	1.8
Dermatological	12	5.4	18	8.1	30	13.5	3	1.4	2	0.9
Superficial edema	8	3.6	4	1.8	12	5.4	5	2.3	0	0.0
Liver toxicity	3	1.4	4	1.8	7	3.2	1	0.5	1	0.5
Body weight changes	3	1.4	14	6.3	17	7.7	6	2.7	1	0.5
Others	12	5.4	3	1.4	15	6.8	0	0.0	1	0.5

Table 3: Period of persistence of adverse events of imatinib in Indian CML-CP patients (n=36)

Adverse events	≤ 4 wks		5wk - 3m		Total ≤ 3m		4m - f/u	
	No.	%	No.	%	No.	%	No.	%
Total (222)	**85**	**38.8**	**58**	**26.1**	**143**	**64.4**	**79**	**35.6**
Hematological	34	15.3	15	6.8	49	22.1	5	2.3
GI disturbances	17	7.7	4	1.8	21	9.5	7	3.2
Musculoskeletal	14	6.3	20	9.0	34	15.3	4	1.8
Dermatologic	12	5.4	8	3.6	20	9.0	15	6.8
Superficial edema	1	0.5	7	3.2	8	3.6	9	4.1
Body weight changes	0	0.0	2	0.9	2	0.9	22	9.9
Liver toxicity	0	0.0	0	0.0	0	0.0	9	4.1
Others	7	3.2	2	0.9	9	4.1	8	3.6

Table 4: Treatment of adverse events of imatinib in Indian CML-CP patients (n=36)

Adverse events	Symptomatic treatment		Specific Treatment		Total	
	No.	%	No.	%	No.	%
	61	**27.5**	**10**	**4.5**	**71**	**32.0**
Musculoskeletal	28	12.6	-	0.0	28	12.6
GI disturbances	19	8.6	-	0.0	19	8.6
Dermatological	13	5.9	1	0.5	14	6.3
Headeche	1	0.5	-	0.0	1	0.5
Pleural effusion	-	-	1	0.5	1	0.5
Superficial edema	-	-	4	1.8	4	1.8
Anaemia	-	-	4	1.8	4	1.8

Table 5: Causality assessment of AEs reported during imatinib therapy in CML-CP patients (n=36) using WHO-UMC system;

Total AEs=222, Total types of AEs = 40

Causality terms	Certain	Probable/likely	Possible	Unlikely	Inaccessible/Unclassifiable
AEs(Total = 222)	46	124	47	2	3
%	20.7	55.9	21.2	0.9	14

None of the AEs was in Conditional/unclassified category

Table 6: Comparison of adverse events of imatinib reported in our study with Western studies [6,7] and Indian studies [10.11]

Common Adverse events (All grades) (% patients)	Our study N = 36 %	Kantarjian[6] N = 532 %	IRIS[7] N=51 %	Arora[10] N =73 %	Deshmukh[11] N =97 %
Weight gain	61.1	30.3	14.3	61.6	38
Edema	47.2	61.1	56.4	49.3	63.9
Muscle cramp	36.1	49.9	39.6	16.7	
Myalgia	30.6	20.2	22.9	27.8	
Skin rash	30.6	35	35.9	14.1	21.6
Hypo pigmentation	27.8	-	-	41.2	73
Dyspepsia	25	17	16.2	16.7	
Nausea	22	56.5	44.4	68	
Arthralgia	22.2	19.8	30.7	20.3	
Fatigue	16.7	18.4	35.6	11.3	
Headache	13.9	13	31.4	19.2	
Pruritus	11.1	9	7.5	5.6	
Vomiting	8.3	23	18.4	-	
Diarrhea	5.6	29	34.6	4.2	
Abdominal Pain	5.6	19	29.4	-	
Hematological					
Thrombocytopenia	61	19.9	64.4	98	17.5
Leucopenia	33.3	23.7	-	63.7	
Neutropenia	33.3	35.1	75.1		20.6
Anemia	22.2	7.1	47.7	37.6	
Elevated liver Enzymes	16.7		43.2	23.6	

Weight gain was the most common non-hematological event reported in more than 60% of patients. Average weight gain was 6.4. kg (median 5.5kg) which ranged from 2 to 14 kg. The common onset of weight gain was between one and 3 months of therapy which continued till the last follow up of the patient. It was of grade I/II mainly, where no treatment and alteration in the therapy were required.

Superficial edema, presented as facial puffiness or per orbital edema and pedal edema, was the 2nd most common non-hematological effect seen in about 50% of patients. It started commonly within 3 months of therapy and continued till the last follow up. Only few patients needed low dose furosemide for unresolved edema and none of them needed drug withhold or dose decrement.

Muscle cramp and myalgia were reported in about one third of patients. Mostly started within the first month of the therapy and persisted for less than 3 months. Almost all of the patients required analgesics for pain relief and none of them needed drug withhold.

Skin rashes were reported in about 30% of patients as papular lesions at upper limbs or back within 3 months of therapy and resolved within one month with symptomatic treatment only, for associated itching.

Hypo pigmentation reported as fair exposed body parts in abut 28% of patients within 3 months of therapy and continued till last follow up. None of them required any treatment or alteration in the therapy.

Nausea and Dyspepsia were reported about 25% of patients within month of therapy and resolved within one month with antacids only.

Arthralgia and general body fatigue were other common non-hematological effects, reported within 3 months of therapy and continued for less than 3 months. Arthralgia required pain killers only while no treatment was needed for fatigue.

Hematological toxicity; Thrombocytopenia was the most common toxicity reported in about 60% of patients. Common onset was within 3 months of therapy which resolved with drug withhold for about 2 weeks but permanent dose decrement was needed in some cases due to recurrence of grade III toxicity. Total leukocyte count with neutropenia an anemia were reported as part of general myelosuppression. Drug was withheld in high grades of neutropenia Iron and folic acid supplementation were given for anemia.

Causality Assessment

Causality assessment of adverse events, reported during the imatinib therapy was done using WHO-UMC System[14] and shown in table 5 .

Discussion

This was a prospective, open-label, non-comparative, and hospital based study in which 36 chronic myeloid leukemia patients in the chronic phase of the disease were started on imatinib mesylate therapy and a total of 222 adverse events were recorded for over 12 months of therapy.

Adverse events in our study (Table 1) can be compared with adverse events reported in Kantarjian study[6], IRIS study[7], Indian studies[10, 11] (table 6) and show differences in frequencies which may be due to different genetic make up of Western and Indian population which respond differently to the drug. Other reasons may be different duration of follow up and sample size of the studies which were lesser in our study as compare to Western studies. Even after so many differences in studies the general trend of the common adverse events reported in our study i.e. weight gain, edema, myalgia, arthralgia, thrombocytopenia is similar to Indian studies. [10,11]

Hypo pigmentation (fair body color) reported in our study is consistent with previous Indian studies which was not reported in landmark Western studies [6,7] may be due to easy appreciation of color change in dark brown color of Indian patients. The hypothesis of pigmentary changes is inhibition of c-Kit imatinib which has a crucial role in melanogenesis, the center of melanocyte homeostasis and of ultraviolet B-induced pigmentation.

Less common adverse events i.e. alopecia, dizziness, weight loss, constipation and anorexia reported in our study were also reported in IRIS study.[7] Hyper pigmentation of body reported in four patients were also reported in four patients was consistent with Arora et al study but not reported in Western studies. Some uncommon adverse events were also reported in the study i.e. nail bed pigmentation in 3 patients which was not reported in IRIS[7] and study by Arora et al[10], pleural effusion in one patient which has been reported in a case report by Breccia et al.[15]

Most of the adverse events (80%) occurred within 3 months of the therapy, were musculoskeletal, gastrointestinal and hematological disturbances mainly and persisted for about one to three months. The early occurrence of these reactions may be attributed to the myelosuppression and some unknown mechanisms for which body develops tolerance within few months. Some early reactions like GI disturbances may be attributed to local irritation of gastric mucosa and stimulation of CTZ in brain. Adverse events, reported after 3 months of therapy and continued till last follow up were weight gain, superficial edema and hypo pigmentation. Fluid retention, the cause of weight gain and edema might be starting early but appreciated at around three months. Tolerance might be developing to these effects also, so initial rise in weight becomes slow in the later stage of the therapy. Hypo pigmentation which has been hypothesized due to inhibition of c-kit gene, which has role in melanogenesis, presents as delayed effect as transcription inhibitors, as evidenced by other molecules, takes weeks to show their effect and appreciable change in body color takes time.

Most of the events were mild to moderate requiring only symptomatic treatment with analgesics for myalgia, arthralgia and cramps in initial days but tolerated well later. Specific therapy was low dose jurosemide for unresolved edema and iron for anemia. These findings are also consistent with previous studies. [6,7,10.11]

Drug was well tolerated and withhold was not needed in 88% of adverse events except in grade II/III thrombocytopenia and grade III neutropenias where it was done for about one to two weeks within initial 3 months of therapy. But in some cases more than two weeks of drug withhold was required and permanent dose decrement was done if toxicity was recurring or not resolving. In Knatarjian et at study[6] , drug was interrupted for 2 weeks and dose was decreased to 300 mg if toxicity was unresolved to

lower grade. Arora et al[10] needed dose interruptions at median duration of 8 weeks and stopped for a median duration of 3 weeks.

Casual relationship of the imatinib mesylate therapy with reported adverse events was established using WHO-UMC criteria. Most of the events (56%) i.e. edema, muscle pain, skin rashes, weight gain, pigmentary changes, were having probable relationship with the imatinib therapy as these could not be explained with the disease, or other concurrent or past drug therapy. Only hematological reactions (21%) were having certain relationship with the therapy because counts recover after drug withhold and fall again on restarting the drug. Rest of the reactions i.e. fatigue, weight loss , anemia, dyspepsia were having possible relationship with the therapy (21%) as these can be explained with both drug therapy as well as disease or concurrent folic acid and iron supplementation.

Conclusion

Imatinib was well tolerated therapy, having only mild to moderate grade of toxicities, mostly within 3 months of therapy and most of them persisted for less than 3 months of duration, requiring only symptomatic treatment and drug withhold or dose decrement in only few cases. Frequency of adverse events was found to be different in Western studies but further studies need to be done for conclusion.

Acknowledgement: The authors thank Dr. Arati Gupta for helping in patient recruitment.

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