

Adverse drug reactions of imatinib in patients with chronic myeloid leukemia: A single-center surveillance study

Jose Francis, Muthiah Palaniappan¹, Biswajit Dubashi², Suresh Chandra Pradhan, Adithan Chandrasekaran¹

Departments of Pharmacology, ¹Clinical Pharmacology and ²Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

Received: 30-07-2014

Revised: 25-10-2014

Accepted: 01-11-2014

ABSTRACT

Objective: To monitor the adverse drug reactions (ADRs) associated with imatinib treatment in patients with chronic myeloid leukemia (CML) in a tertiary care hospital. **Materials and Methods:** The study was carried out by the Departments of Pharmacology and Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. The study was carried out from March 2012 to February 2014. The ADRs were reported in a suspected Adverse Drug Reaction Reporting form, provided by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health and Family Welfare, Government of India. The ADRs were analyzed for their pattern, causality and severity. **Results:** A total of 326 ADRs from 81 patients were reported during the study period. The hematological toxicities were much more prominent than the non-hematological toxicities in this study. The prevalence of thrombocytopenia (21.17%) was higher compared with other reactions. Further analysis showed that most of the ADRs were mild to moderate in nature. The causality assessment revealed that the majority of the ADRs belonged to the possible category. **Conclusion:** The present study in a tertiary care hospital suggests that hematological toxicities are predominant in CML patients treated with imatinib mesylate. The blood and lymphatic system (38.96%) was the most affected, with imatinib therapy and thrombocytopenia (21.17%) being the most commonly encountered ADRs in the present study. Thorough monitoring of ADRs is warranted for better treatment outcomes.

Key words: Adverse drug reactions, chronic myeloid leukemia, hematological toxicities, imatinib mesylate, thrombocytopenia

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.149141

INTRODUCTION

Imatinib mesylate is a specific small molecule tyrosine kinase inhibitor that has profoundly improved the prognosis of chronic myeloid leukemia (CML). It selectively inhibits Breakpoint cluster region –Abelson leukemia (BCR-ABL) oncogene, a constitutively active tyrosine kinase that is virtually present in almost all of the CML patients.^[1] Treatment

Address for correspondence:

Jose Francis, Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry - 605 006, India. E-mail: josefrancis123@gmail.com

with imatinib usually continues for the entire lifespan, and is well tolerated in most of the patients. As the treatment endures for their life span, majority of the patients experience drug-related adverse effects at some point or other of their treatment course.^[2] The majority of these imatinib-related adverse drug reactions (ADRs) are of mild to moderate in nature and often reversible by supportive care or temporary cessation of treatment.^[3] Most of these drug-related ADRs are associated with the hematological system or musculoskeletal system.^[2,4]

Much of the information related to drug safety is acquired through pharmacovigilance.^[5] Incidences of drug-related adverse effects in a large population are often gathered through pharmacovigilance programs. The ADR profile of imatinib has been reported from Western studies, which show that the hematological and musculoskeletal systems were the most commonly affected.^[2,6] Previous reports from India show varied frequencies of adverse events compared with the Western studies.^[7-9]

Considering these aspects, the present study was the surveillance of the ADRs associated with the use of imatinib in CML patients. Further, the ADR information collected was assessed using the World Health Organization scale for their causality and the Hartwig scale for the severity of their reactions.^[10,11]

MATERIALS AND METHODS

Study cohort

The study was carried out by the Department of Pharmacology and Medical Oncology, JIPMER, Puducherry, India. This prospective surveillance of ADRs was conducted from March 2012 to February 2014. All patients who were diagnosed as cases of CML (presence of Philadelphia chromosome) and experienced any adverse effect during their treatment course only were included in the analysis. The study was approved by the Institute Ethics Committee of the JIPMER, Puducherry, India.

Data collection

The ADRs were reported in a Suspected Adverse Drug Reaction Reporting form provided by the CDSCO, Ministry of Health and Family Welfare, Government of India. The ADR data were collected by a patient case sheet review including medication history and clinical examination (physical, biochemical and hematological parameters).

Data analysis

The ADRs were analyzed for the pattern of reaction, causality of the ADRs and the severity of the reaction. The causality of the ADRs was analyzed by the WHO Causality Assessment Scale. The severities of ADRs were analyzed using the

Modified Hartwig Siegel's Severity Assessment Scale, which categorizes ADRs as mild, moderate and severe.

RESULTS

Patient demographics

A total of 119 patients were diagnosed to be having CML and were started on imatinib treatment, of whom 81 patients (68.07%) experienced various adverse events during their treatment course. The mean age group of the study cohort was 39.93 years (17–74 years). The mean body weight of the study population was 53.03 kg (31–88 kg). Of 119 patients, 111 patients were on 400 mg and the remaining ($n = 8$) were on 600 mg daily dosage. None of the patients who suffered any adverse events were on any co-medication that could significantly interact with imatinib.

Incidence and analysis of ADSs

A total of 81 patients presented with 326 ADRs (no. of reports = 251). About 54.4% of the total ADR reports corresponded to males and 45.6% to females. Of the hematological toxicities, platelet was the predominant blood component to be affected, with thrombocytopenia accounting for 21.17%, followed by leukopenia (8.28%) and anemia (5.52%). Myalgia was the frequently reported musculoskeletal adverse event (7.36%). Some of the uncommon dermatological complications that occurred include petechial spots, acneiform rash and pruritus. There were minimal reports of adverse events associated with the nervous and psychiatric systems.

The ADRs reported were classified according to CTCAE (Common Terminology Criteria for Adverse Events Ver 4.03)^[12] and are presented in Table 1. The manifestation of ADRs commonly involved blood and lymphatic system, with $n = 127$ (38.96%), followed by the musculoskeletal system, with $n = 64$ (19.63%). The skin and subcutaneous system and

Table 1: Classification of ADRs with CTCAE

System organ class	No. of ADRs ($n=326$)	Percentage
Blood and lymphatic system disorders	127	38.96
Musculoskeletal and connective tissue disorders	64	19.63
General disorders and administration site conditions	43	13.19
Skin and subcutaneous tissue disorders	35	10.74
Gastrointestinal disorders	30	9.20
Investigations (weight gain)	21	6.44
Nervous system disorders	3	0.92
Psychiatric disorders	2	0.61
Immune system disorders	1	0.31

CTACE=Common Terminology Criteria for Adverse Events

general and gastrointestinal toxicities were the other commonly reported events in the present study.

The ADRs were then scrutinized for their causality and severity and are presented in Figure 1. The causality assessment using the WHO-UMC scale showed that most of the adverse events were of possible category (56.8%), followed by certain (33.1%) and probable (10.4%). The severity assessment using the Hartwig scale revealed that most of the events were mild (67.6%), followed by moderate (30.1%) and severe (2.7%) reactions. In the present study, there were no deaths reported due to imatinib treatment.

Further, the hematological toxicities were assessed and graded using CTCAE Ver 4.03, which revealed that most of them belong to Grades I and III thrombocytopenia ($n = 33$ and 16 in each group). The grade of hematological toxicities is presented in Table 2. Except for some of the hematological toxicities, all others were mild to moderate in nature (Grades I/II). The common adverse events observed in the present study were compared with the previously published results, and are depicted in Table 3.

DISCUSSION

Imatinib mesylate is presently considered as first-line treatment in CML patients. Imatinib being a small molecule tyrosine kinase inhibitor targeting specific BCR-ABL kinase, the tolerability is good with less adverse events compared with other cytotoxic anticancer agents.^[2] The adverse events mostly occur during the initial stage of therapy, and their extent depends on the phase of the disease and the dose given.

Various studies have explored the drug-related toxicities of imatinib that have shown the hematological, musculoskeletal and gastrointestinal systems to be the commonly affected systems.^[2,3,6] The present study results also lie in partial

agreement with the previously published results [Table 3]. Some of the commonly encountered ADRs in the present study were compared with other published results. However, there is a difference in the frequency of adverse events of the present study with the western studies.^[2,6] The reason behind this may be due to the distinct genetic makeup of populations involved in the studies. The comparison with other Indian studies showed that the incidence of myalgia is almost similar across different study groups. But, the frequencies of thrombocytopenia and hypopigmentation were varying when compared with other Indian studies.^[7-9] However, the changes in the frequency of ADRs may be due to the different size of populations in various studies mentioned ($n = 36-450$), which cannot be ruled out.

The adherence to imatinib is a major factor for optimal therapeutic success. Various studies explored the major reasons for non-adherence, of which adverse events played a major role in causing non-adherence.^[13,14] Adverse effects of imatinib play a pivotal role in determining adherence to treatment, thereby affecting treatment response. Therefore, vigilant monitoring of adverse events has a role in determining treatment success.

The management of adverse drug reactions that occurred in the study was treated according to the previously published guidelines.^[15,16] The management of the adverse drug reactions usually involved temporary cessation of imatinib usually in the case of Grade III and Grade IV hematological toxicities. Dose modification was warranted for few patients due to persistent hematologic toxicities. Most of the ADRs were encountered during the initial 3 months of the imatinib treatment, which is in accordance with studies published elsewhere.^[3] None of the patients was discontinued from imatinib therapy due to toxicities. The long-term adverse events seen in this patient cohort were insomnia and dermatological complications like palmar-plantar dysesthesia, acneiform rash and petechial spots.

CONCLUSION

The present study illustrates the pattern of adverse events in south Indian CML patients who were on imatinib therapy. Thrombocytopenia was the most common adverse effect with a percentage occurrence of 57.9%, which is midway between

Table 2: Grade of hematological toxicities

Hematological toxicity	Grade I	Grade II	Grade III	Grade IV
Anemia ($n=18$)	3	7	7	1
Leukopenia ($n=27$)	14	9	4	-
Thrombocytopenia ($n=69$)	33	13	16	7

Table 3: Comparison of the incidence of common ADRs in the present study with other published results

Common ADRs	Present study ($n=119$) (%)	O'Brien <i>et al.</i> ^[2] ($n=51$) (%)	Kantarjian <i>et al.</i> ^[6] ($n=450$) (%)	Arora <i>et al.</i> ^[7] ($n=73$) (%)	Deshmukh <i>et al.</i> ^[8] ($n=97$) (%)	Meena <i>et al.</i> ^[9] ($n=36$) (%)
Thrombocytopenia	57.9	64.4	19.9	98	17.5	61.0
Myalgia	20.2	22.9	20.2	27.8	-	30.6
Weight gain	26.9	14.3	30.3	61.6	38	61.1
Leukopenia	22.7	-	23.7	63.7	-	33.3
Hypopigmentation	17.7	-	-	41.2	73	27.8

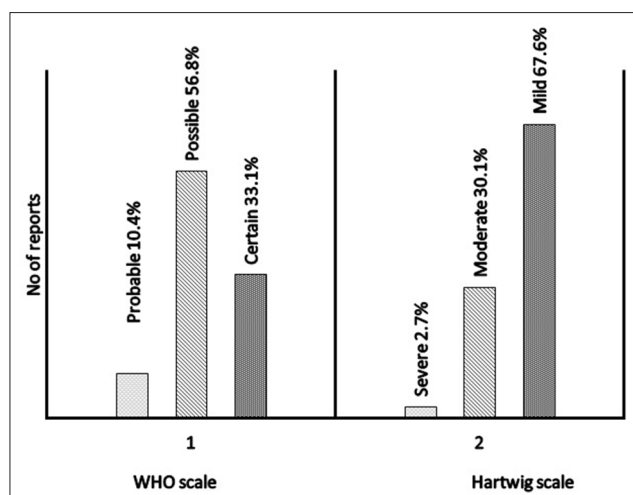


Figure 1: Causality (WHO scale) & Severity (Hartwig scale) assessment of ADRs the present study

the frequency reports in earlier Indian studies (17.5%–98.0%). The monitoring and management of adverse events associated with imatinib therapy are warranted for better treatment outcomes.

REFERENCES

1. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344:1031-7.
2. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, *et al.*; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348:994-1004.
3. Thanopoulou E, Judson I. The safety profile of imatinib in CML and GIST: Long-term considerations. *Arch Toxicol* 2012;86:1-12.
4. Ramanathan RK, Egorin MJ, Takimoto CH, Remick SC, Doroshow JH, LoRusso PA, *et al.* National Cancer Institute Organ Dysfunction Working Group. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: A study by the National Cancer Institute Organ Dysfunction Working Group. *J Clin Oncol* 2008;26:563-9.
5. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother* 2013;4(Suppl 1):S73-7.
6. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, *et al.*; International STI571 CML Study Group. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002;346:645-52.
7. Arora B, Kumar L, Kumari M, Sharma A, Wadhwa J, Kochupillai V. Therapy with imatinib mesylate for chronic Myeloid Leukemia. *Indian J Med Paediatr Oncol* 2005;26:5-16.
8. Deshmukh C, Saikia T, Bakshi A, Amare-Kadam P, Baisane C, Parikh P. Imatinib Mesylate in chronic myeloid leukemia: A prospective, single arm, non-randomized study. *J Assoc Physicians India* 2005;53:291-295.
9. Meena R, Biswas NR, Kumar L, Velpandian T, Gupta YK. Safety profile of imatinib in Indian chronic myeloid leukemia patients. *Health Renaissance* 2011;9:24-30.
10. The Use of the WHO-UMC System for Standardised Case Causality Assessment. Available from: <http://www.who-umc.org/Graphics/26649.pdf>. [Last accessed on 2012 Apr 17].
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992;49:2229-32.
12. Common Terminology Criteria for Adverse Events (CTCAE). Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5_x_11.pdf. [Last accessed on 2013 Aug 23].
13. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachée P, Berneman Z, *et al.* Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study. *Blood* 2009;113:5401-11.
14. Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, *et al.* Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol* 2010;10:2381-8.
15. Jabbour E, Deininger M, Hochhaus A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. *Leukemia* 2011;25:201-10.
16. Mauro MJ, Deininger MW. Management of drug toxicities in chronic myeloid leukaemia. *Best Pract Res Clin Haematol* 2009;22:409-29.

How to cite this article: Francis J, Palaniappan M, Dubashi B, Pradhan SC, Chandrasekaran A. Adverse drug reactions of imatinib in patients with chronic myeloid leukemia: A single-center surveillance study. *J Pharmacol Pharmacother* 2015;6:30-3.

Source of Support: Nil, **Conflict of Interest:** None declared.