



Original Article

Social and Financial Barriers to Optimum TKI Treatment in Patients with Chronic Myeloid Leukemia- A Knowledge-Attitudes-Practices Study from India

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Abstract. Introduction: Outcomes in chronic myeloid leukemia (CML) have vastly improved after introducing tyrosine kinase inhibitors. However, patients in low and middle-income countries (LMICs) face many challenges due to social and financial barriers.

Objective: This study was conducted to understand socio-economic hindrances, knowledge-attitudes-practices, and assessing nonadherence to treatment in chronic phase CML patients taking imatinib.

Materials and Methods: Patients of chronic phase CML, aged 15 and above, taking imatinib for six months or more were included in the study. A questionnaire (in the Hindi language) was administered, inquiring about the nature of the disease and its treatment, how imatinib was obtained, drug-taking behavior, and the treatment's economic and social burden. Nonadherence was assessed by enquiring patients for missed doses since the last hospital visit and for any treatment interruptions of ≥ 7 days during the entire course of treatment (TIs).

Results: Four hundred patients were enrolled (median age 37 years, median duration on imatinib 63 months). Patients hailed from 16 different Indian states, and 29.75% had to travel more than 500 kilometers for their hospital visit. Scheduled hospital visits were missed by 14.75%. A third of the patients were unaware of the lifelong treatment duration, and 41.75% were unaware of the risks of discontinuing treatment. Treatment was financed by three different means- 61.75% received imatinib via the Glivec International Patient Assistance Program (GIPAP), 14.25% through a cost-reimbursement program, and 24% self-paying. 52.75% of patients felt financially burdened due to the cost of drugs (self-paying patients), cost of investigations, the expenditure of the commute and stay for the hospital visit, and loss of working days due to hospital visits. 41.25% of patients reported missed doses in the last three months, and 9% reported missing $>10\%$ doses. 16.5% of patients reported TIs. Nonadherence $>10\%$ and TIs were significantly higher in self-paying patients (15.6% and 25% respectively).

Conclusion: We observed that patient awareness about the disease was suboptimal. Patients felt inconvenienced and financially burdened by the treatment. Nonadherence and treatment interruptions were observed in 41.25% and 16.5%, respectively. These issues were prevalent in self-paying patients.

Keywords: Chronic myeloid leukemia; Cost of treatment; GIPAP; Nonadherence.

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Introduction. The long-term prognosis of chronic myeloid leukemia (CML) underwent a revolutionary change since the introduction of tyrosine kinase inhibitors (TKIs). These agents have altered CML's natural history and changed it from a fatal disease into a chronic disease with lifelong treatment. Thousands of CML patients across the globe are currently taking one of the TKIs. However, treating CML in low and middle-income countries (LMICs) is still challenging owing to issues with patient awareness, delayed diagnosis, and poor access to treatment. The current study was conducted to understand knowledge-attitudes-practices of patients of CML who are taking imatinib.

Study Methodology. This study was a single-center cross-sectional observational study conducted from 1st May 2017 to 31st July 2018 at the Hematology clinic of a public sector tertiary hospital in North India. Consecutive patients of chronic phase CML, aged 15 and above, who had been taking imatinib for six months or more, were enrolled in the study. Patients in accelerated phase or blast phase and those who were taking treatment other than imatinib were excluded. Prior approval from the Institutional Ethics Committee was obtained. All procedures followed were in accordance with the responsible committee's ethical standards on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Clinical history and examination findings, along with demographic data and treatment procedures, were recorded. The investigator administered a questionnaire (in the Hindi language); wherein patients were asked about their perceptions of the nature of the disease and its treatment, how imatinib was obtained, drug-taking behavior, the economic and social burden of the treatment. The patient reported nonadherence was recorded by enquiring the percentage of missed doses since the last hospital visit and episodes of treatment interruptions (TIs) of ≥ 7 days (at any point during treatment).

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean \pm SD and median. The normality of data was tested by the Kolmogorov-Smirnov test. If the normality was rejected, then the non parametric test was used. Quantitative variables were compared using the Kruskal Wallis test for more than two groups. Qualitative variables were correlated using the Chi-Square test. A p-value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet, and analysis was done using Statistical Package for Social Sciences (SPSS) version

21.0.

Results. A total of 400 patients were enrolled. Demographic data is presented in **Table 1**. The median age of the study group was 37 years, with a higher number of male patients. The median duration on imatinib was 63 months. The study group comprised patients from varied educational backgrounds, and 18.25% of the patients were illiterate. Patients hailed from 16 different states, with the largest numbers hailing from Uttar Pradesh, Delhi, Haryana, and Bihar. Roughly one-third of the patients had to travel more than 500 kilometers (each side) for their hospital visit with a travel duration of >12 hours each side. Patients lost a median of 2 workdays for each hospital visit. Scheduled hospital visits were missed by 14.75% of patients.

Table 1. Demographic and social data

Parameter	
Age (median; range) years	37 (15-76)
Age groups (years)	
15 – 20	18 (4.50%)
21 – 30	78 (19.50%)
31 – 40	148 (37.00%)
41 – 50	98 (24.50%)
51 – 60	35 (8.75%)
>60	23 (5.75%)
Sex (M: F)	1.94:1
Education	
Illiterate	73 (18.25%)
Up to 8th	91 (22.75%)
9th-12th	155 (38.75%)
College	81 (20.25%)
Distance travelled per visit	
<100 km	157 (39.25%)
100-500 km	124 (31%)
>500 km	119 (29.75%)
Hours of travel per visit	
<3	147 (36.75%)
3-12	135 (33.75%)
>12	118 (29.5%)
Median number of days of loss of work per visit	2 (range 0-15)
Scheduled hospital visit missed	59 (14.75%)
Median duration of treatment (months)	63 (range 6-194)

Patient awareness about the disease and treatment is described in **Table 2**. The disease's nature was thought to be a "blood infection" by 23 patients (5.75%). A third of the patients were unaware of the lifelong nature of the treatment. One hundred sixty-seven patients (41.75%) were unaware of the risks of interrupting treatment. Drug-taking practices are mentioned in **Table 3**. A fixed routine for taking the drug was followed by 94.25% of the patients, and nearly two-thirds preferred to take the drug at bedtime. 27% of the patients relied on reminders

Table 2. Knowledge about disease and treatment.

Question	Response
1. Do you feel you have been explained about the disease? • Yes • No	358 (89.5%) 42 (10.5%)
2. What is the nature of your disease? # • Blood cancer • Disease of the spleen • Blood infection • Others • Don't know	346 (86.5%) 10 (2.5%) 23 (5.75%) 4 (1%) 32 (8%)
3. Do you know the name of your disease? • Yes (CML) • No	186 (46.5%) 214 (53.5%)
4. What is the treatment of the disease? # • Oral tablets • Bone marrow transplant • Blood transfusions • Don't know	344 (86%) 2 (0.5%) 0 56 (14%)
5. Do you know the name of the tablet given for this disease? • Yes • No	216 (54%) 184 (46%)
6. Till what duration are you supposed to take these tablets? • Lifelong • Till resolution of symptoms • Till doctor advises • Fixed duration • Don't know	265 (66.25%) 9 (2.25%) 35 (8.75%) 17 (4.25%) 74 (18.5%)
7. Are you aware of the risks of stopping treatment? • Yes • No	233 (58.75%) 167 (41.75%)

#- Multiple answers allowed so total can exceed 100%

from family members to take the drug every day. One hundred eighteen (29.5%) patients felt inconvenienced by the treatment, and that was due to a combination of adverse drug effects, treatment financial burden and to the need for regular lifelong follow-up and treatment.

Imatinib was obtained through three different means (**Table 4**). The majority (61.75%) obtained imatinib under the Glivec International Patient Assistance Program (GIPAP). This group of patients received imatinib free of cost from a designated GIPAP center in Delhi. They had to bear the cost of investigations by themselves. The second group (14.25%) of patients obtained imatinib through a cost-reimbursement program which covered all treatment-related expenses. The third group (24%) were self-paying patients who had to bear the entire treatment cost themselves. The GIPAP group received Glivec, and the other two groups of patients received generic imatinib. The median annual treatment related expenditure was highest in the self-paying group of patients, followed by the GIPAP group. The majority of self-paying patients felt that the treatment was a significant financial burden. 44.4% of patients in the GIPAP group also felt the treatment was a financial burden due to the cost of investigations,

Table 3. Drug taking practices.

Question	Response
1. At what time do you take imatinib? • Morning- 58 (14.5%) • Afternoon- 44 (11%) • Night- 263 (65.75%) • Split dose- 12 (3%) Variable timing- 23 (5.75%)	Fixed routine – 377 (94.25%) Variable timing- 23 (5.75%)
2. Do you get reminded by family members to take the tablet?	Y- 108 (27%) N- 292 (73%)
3. Are you taking oral medicines for other diseases?	Y- 51 (12.75%) N- 87.25%
4. Do you feel it is an inconvenience taking tablets daily?	Yes- 118 (29.5%) No- 282 (70.5%)

the expenditure of the commute for the visit, and loss of employment due to hospital visits. Monitoring BCR-ABL IS by quantitative PCR (at any point during follow-up) was done by 76% of patients. Among the three groups, the GIPAP group had the maximum number of patients (30%) who had not tested even once during follow-up.

One hundred sixty-five patients (41.25%) reported missing a dose of imatinib since the last hospital visit. The frequency of hospital visits was once in 3 months. Thirty-six patients (9%) had missed more than 10% of doses. Sixty-six patients (16.5%) reported treatment interruptions of 7 days or more (at any time during treatment). The self-paying patients had significantly higher nonadherence rates (15.6%) and treatment interruptions (25%). (**Table 4**)

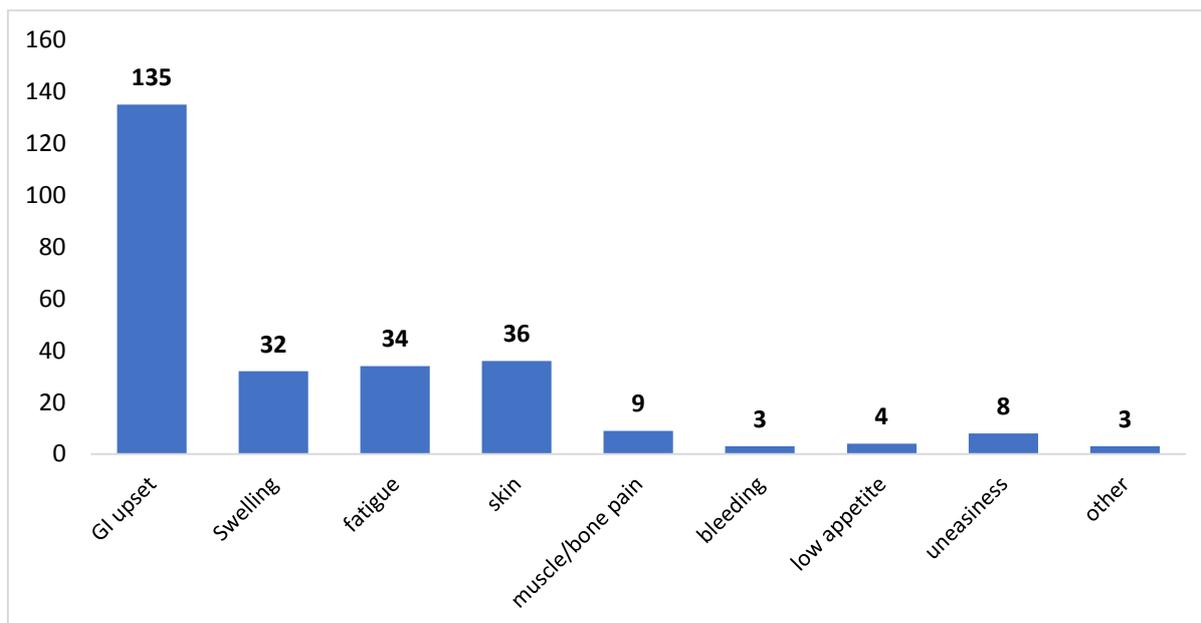
Most common treatment-related adverse effects were gastrointestinal (nausea, vomiting, and decreased appetite), followed by skin hypopigmentation and fatigue. (**Figure 1**)

Discussion. Majority of the patients at public sector hospitals in LMICs hail from the lower socioeconomic strata in whom education levels are low, as reflected by a large number of illiterate patients in our study group. Our study group's education status was similar to that observed in another Indian study¹ and lower than those from Italy² and Brazil.³ The study population comprised patients of 16 states, and a large number of them had to undertake lengthy travel for each hospital visit. Hamerschlag et al. made similar observations in a study from Brazil.⁴ The lack of availability of hematology/oncology specialists in smaller towns coupled with imatinib's unavailability at these centers leads to aggregation of patients at tertiary hospitals in metro cities. The long duration of travel leads to loss of work, and the cost of travel and accommodation further adds to treatment-related expenditure and leads to patient dissatisfaction. The costly and cumbersome

Table 4. Financial impact of treatment.

	GiPAP	Reimbursable	Self-paying	p
n	247 (61.75%)	57 (14.25%)	96 (24%)	
Median annual cost of treatment (INR)	3,000 (range 250 – 60,000)	0 (range 0 – 6,000)	40,000 (range 7,500 – 1,00,000)	<0.0001
"Is treatment a financial burden?"	110 (44.5%)	17 (29.8%)	84 (87.5%)	<0.0001
BCR ABL tested during follow up	173 (70.0%)	52 (91.2%)	79 (82.3%)	0.0009
Missed hospital visits	30 (12.15%)	7 (12.29%)	22 (22.9%)	0.035
Non-adherence (>10%)	17 (6.89%)	4 (8.5%)	15 (15.6%)	0.034
Treatment interruptions of >7 days	36 (14.57%)	6 (10.5%)	24 (25%)	0.027

Figure 1. Treatment related adverse effects (alone or in combination).



nature of hospital visits also leads to the patient missing their scheduled hospital visits.

Patient awareness regarding disease and treatment has been suboptimal in studies from India¹ and Brazil,⁴ whereas it was much better in studies from Europe.^{2,5} We observed low patient awareness regarding the nature of the disease and treatment, particularly regarding treatment duration. This poor information is a peculiar challenge faced during the treatment of CML in low and middle-income nations, particularly in the public sector, where many patients belong to the lower socioeconomic strata and are less educated. Patient awareness is a critical component in ensuring optimum treatment as lack of adequate knowledge about the disease adds to patient anxiety, hampers adherence to treatment, and creates a trust deficit between the patient and the physician.⁶ These findings reiterate the need for focused and easy-to-understand counseling at diagnosis and its repeated reinforcement during subsequent visits.

Patients tend to adopt various practices to make the daily intake of drugs regular and convenient. We observed that most patients followed a regular routine, and many relied on reminders from family members. Similar practices have been reported previously as

well.^{2,7} Studies from India have reported a lower incidence of comorbid ailments⁸ than what is observed in developed nations,⁹ and that can be attributed to a younger CML patient population in India.

Many of our patients reported that the treatment caused them inconvenience due to a combination of various factors- adverse drug effects, the financial burden of treatment, and the need for regular lifelong follow-up and treatment. This vital issue can get these patients demotivated and may induce them to discontinue treatment.

The financial impact of cancer treatment is immense, and it remains one of the most important issues that patients have to take into consideration while going for treatment.¹⁰ The GiPAP program, launched in 2001, provides free of cost Glivec to thousands of patients across the globe. It has been a boon for patients of CML in low-income countries. The greatest beneficiaries of the program have been from India.¹¹ New patients were being enrolled in the program till 2016, and almost all CML patients at our center prior to this got their drug through GiPAP. This group comprises the major bulk of CML patients at our center and it is reflected in the study population with 62% enrolled under GiPAP. We

observed that treatment led to a substantial financial burden in our study group. The median annual treatment related expenditure was highest in the self-paying patients, for whom the cost of imatinib made up the bulk of the treatment expenditure. A large number of GIPAP patients also felt financially burdened by the treatment accessories related to the cost of investigations, travel and accommodation for the hospital visit, and loss of employment. The expenses are comparatively lower than other countries¹⁰ but still substantial for a country with an average annual per capita income of INR 92,565.¹²

The cost of BCR-ABL quantitative estimation by PCR is around INR 6,000- 7,000. This is almost two times the cost of monthly generic imatinib. The unaffordability of repeated BCR-ABL estimations is reflected by the high number of patients who did not get even a single estimation done in the follow-up. This tendency is true even in developed countries, and regular disease assessment either by cytogenetics or molecular methods is infrequently seen outside the setting of clinical trials.^{13,14}

Nonadherence to TKI therapy is a major hindrance to obtaining favorable long term outcomes in patients with CML.^{15,16} The nonadherence patient-reported is a less sensitive methodology for assessing nonadherence as it may underestimate the actual prevalence. Despite this, we observed that a large number of patients were non-adherent to imatinib, and also that many patients reported lengthy treatment interruptions. Previous studies from India have observed nonadherence rates of 25% to 55%.^{1,8,15} The proportion of nonadherence >10% and TIs was significantly higher in the self-paying patients, concerning the financial difficulties faced by

these patients.

Managing CML in low and middle-income countries requires careful titration of the treatment according to the patients' socioeconomic status. All avenues of financial support from both government and non-government schemes must be pursued to ensure uninterrupted treatment.¹⁷ The excellent survival rates of patients under the GIPAP program are a testament to the fact that by improving accessibility to TKIs in LMICs, we can produce results comparable to high-income countries.¹⁸ The availability of TKIs must be coupled with better penetrance of hematology/oncology services to smaller towns and cities and an emphasis on better patient education and treatment adherence.

Our study has several limitations. Patients were assessed at only a single time point without follow up. The disease's awareness would depend upon the initial patient counselling and education that might not be uniform for all patients. The patient-reported nonadherence was assessed over a 3-month duration, which is a less sensitive method and underestimates the actual nonadherence.

Conclusions. This study highlights the major challenges encountered in TKI-based treatment of CML in low and middle-income countries. Inadequate patient education status contributes to suboptimal awareness about disease and treatment. Lack of hematology/oncology services in most parts of the country, costs of drugs and investigations pose a significant financial burden on the patients. Nonadherence (>10% of doses) and treatment interruptions were observed in 9% and 16.5% of patients respectively. These were significantly higher in self-paying patients.

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