

Review Article

Non-adherence to CML therapy and its clinical implications in India

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ABSTRACT

Clinical trials have shown that early and deeper cytogenetic/molecular responses to tyrosine kinase inhibitors (TKIs) help in achieving improved long-term outcomes including lower rates of disease progression in chronic myeloid leukaemia (CML). However, the level of molecular responses achieved with TKI therapy in patients with CML is variable and this could be explained by differences in adherence to CML therapy. A systematic literature review of CML studies reporting adherence to BCR-ABL inhibitors from the USA, Asia and Europe (19 articles: 9 retrospective, 4 prospective, rest cross-sectional) showed that average adherence varies from 19% to 100% of the proportion of prescribed drug taken. Some factors that contribute to non-adherence include patient attitudes, adverse events associated with therapy, treatment complexities and socioeconomic issues. This article focuses on the problem of non-adherence to therapy in CML, especially from an Indian perspective, and offers suggestions for its mitigation.

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INTRODUCTION

Chronic myeloid leukaemia (CML) is a haematopoietic stem cell disease characterized by the presence of a specific chromosome (Philadelphia chromosome) and its corresponding molecular marker BCR-ABL fusion transcripts (tyrosine kinase proteins). The management of CML was revolutionized by the advent of targeted therapy, the tyrosine kinase inhibitors (TKIs). Imatinib was the first TKI to be approved for CML in 2001, followed by more potent BCR-ABL inhibitors, nilotinib and dasatinib. All three drugs are now approved for initial therapy of CML. BCR-ABL fusion transcripts provide a suitable tool to monitor the disease burden in CML. Studies have shown that the prognosis is linked to cytogenetic and molecular responses and achieving specific degrees of disease reduction at specific time points is an essential part of CML management.¹ The success of TKI treatment is determined by continuous optimal dosing and strict treatment adherence. Imatinib boosts the overall survival at 8 years to 85% in patients adhering to treatment.² Clinical trials have shown that early and deeper cytogenetic/molecular responses to TKIs help in achieving early undetectable BCR-ABL transcripts resulting in

improved long-term outcomes including lower rates of disease progression. In the landmark IRIS (International Randomized Study of Interferon and STI571) study, patients who achieved major cytogenetic response (MCyR) by 3 months had a longer time to disease progression during the subsequent 12 months.³ In another study, the probability of achieving complete cytogenetic response (CCyR) or major molecular response (MMR) decreased steadily with time if CCyR was not achieved by 3, 6 or 12 months.⁴ The National Comprehensive Cancer Network (NCCN) Guidelines recommend achievement of BCR-ABL transcript level $\leq 10\%$ as the 3-month treatment response goal.^{5,6} Thus, adherence is crucial in the first 18 months of treatment as achieving a deep level of response within this timeframe produces better long-term outcomes. Moreover, to maintain the response, patients need prolonged period of treatment. Long-term IRIS follow-up studies have shown that imatinib's therapeutic benefits extend up to 7 years and longer in patients with CML who get uninterrupted treatment.⁷

Approximately 40% of patients who remain on imatinib for more than 5 years will have undetectable minimal residual disease (UMRD).⁸ Therefore, continued compliance throughout life is of utmost importance for better clinical outcomes. The European LeukemiaNet management guidelines for CML recommend continuing TKI indefinitely in responding patients, even in those with UMRD.⁹

IMPLICATIONS OF POOR ADHERENCE ON DISEASE OUTCOMES

With the current recommendation of 'indefinite or lifelong TKI therapy in CML for maximum benefits' issues related to treatment adherence become particularly important. Adherence is defined as the extent to which patients are able to follow the recommendations for prescribed treatments.^{10,11} Studies of adherence in patients with non-cancer medical conditions (diabetes, hypercholesterolaemia, hypertension) requiring chronic medications have shown that adherence to medications is poor (20% to 50%) and about half the patients discontinue therapy within the first 6 months of treatment.¹² It is a misconception that cancer, because of its grave severity, may be associated with better adherence to therapy. Non-adherence to BCR-ABL inhibitors in CML is common; studies have shown that non-adherence in CML is a serious problem, with a quarter to one-third of patients being non-adherent.^{10,11} Non-adherence is associated with unfavourable outcomes including suboptimal treatment responses, imatinib resistance, disease relapse and increase in healthcare costs (Table I).¹³⁻¹⁶ In the Hammersmith Hospital study, Marin *et al.* reported that patients with $\leq 90\%$ adherence were significantly less likely

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TABLE I. Studies evaluating adherence to treatment and its clinical implications in patients with chronic myeloid leukaemia (CML)

Author (year)	Brief study description	Reported adherence to therapy
Noens <i>et al.</i> (2009) ¹³	Prospective observational ADAGIO (Adherence assessment with Glivec: Indicators and outcomes) study; Adherence was analysed in 169 CML patients during a 90-day period and correlated with overall treatment responses	<ul style="list-style-type: none"> • 14% (based on pill counts: 100% of imatinib taken) • Adherence in patients with partial cytogenetic response: 74%–77% • Adherence in patients with complete cytogenetic response (CCyR): 90%–93%
Wu <i>et al.</i> (2010) ¹⁴	Retrospective analysis and 6-month follow-up analysis combining two retrospective databases of patients receiving dasatinib ($n=452$) or nilotinib ($n=69$); Adherence measured by proportion of days covered (PDC)	<ul style="list-style-type: none"> • Nilotinib: mean (SD) PDC: 0.79 (0.23) • Dasatinib: mean (SD) PDC: 0.69 (0.28); $p=0.009$
Ibrahim <i>et al.</i> (2011) ¹⁵	Relation between adherence to imatinib and the probabilities of losing CCyR and of imatinib failure in 87 CCyR CML patients receiving long-term therapy	<ul style="list-style-type: none"> • Probability of losing CCyR at 2 years\ • patients with adherence rate $\leq 85\%$: 26.8% • patients with adherence rate $>85\%$: 1.5%; $p=0.0002$
Noens <i>et al.</i> (2014) ¹⁶	Systematic literature review of CML studies reporting adherence to BCR–ABL inhibitors from the USA, Asia and Europe (19 articles: 9 retrospective, 4 prospective, rest cross-sectional)	<ul style="list-style-type: none"> • 19% to 100% (varied with study groups and measurement methods) • Retrospective cohort: <ul style="list-style-type: none"> • Nilotinib: 79% • Dasatinib: 69% • In another cohort in the analysis, patients receiving second-line nilotinib were two times more likely to have poor adherence compared to dasatinib

to achieve MMR or complete molecular response (CMR) than were patients with $>90\%$ adherence. No molecular responses were observed when adherence was $\leq 80\%$ ($p<0.001$).¹⁷ Patients whose imatinib doses were increased were found to have poor adherence (86.4%); adherence was the only independent predictor for inability to achieve an MMR (RR 17.66, $p=0.006$).¹⁷ Poor adherence may lead to loss of treatment response. In one study, patients who had $\leq 85\%$ adherence to imatinib were significantly more likely to lose CCyR at 2 years and experience treatment failure than patients with $>85\%$ adherence.¹⁵ Studies evaluating adherence to second-line BCR–ABL TKIs are few. Dasatinib with its once daily regimen may have better compliance compared to nilotinib, which is taken twice daily. In a retrospective study published in 2012, patients receiving second-line nilotinib had poorer adherence compared to those taking dasatinib (100 mg once daily). No correlation was found between adherence and treatment response.¹⁸

In India, there are few published studies on assessment of treatment adherence in CML. In a retrospective analysis using the Glivec International Patient Assistance Program (GIPAP) database, 29.6% of patients were not completely adherent to imatinib and, in a multivariate analysis, non-adherence was the only factor significantly affecting event-free survival (EFS). The overall estimated 5-year EFS rate was 70.8% (95% CI 63.3–78.3) with a median follow-up of 39 months. The 5-year EFS rate in adherent patients was 76.7% compared to 59.8% ($p=0.011$) in non-adherent patients, pointing to the impact of adherence on survival.¹⁹ An analysis of unpublished data from Tata Memorial Centre, Mumbai among 1074 patients with CML (year 2004–09) showed that almost 26% of patients receiving Glivec through an access programme were non-adherent to therapy. However, the non-adherence was much higher among those receiving Glivec through an access programme compared to those receiving generic imatinib, indicating that factors other than cost are key contributors to non-adherence. It was also seen that overall treatment interruptions were far higher in those who did not achieve a CCyR (37.7%, $n=242$) as compared to those who did (21.4%, $n=832$) (personal communication).

MEASURING ADHERENCE TO THERAPY

There are several methods to measure adherence though none of them is absolutely accurate. The ADAGIO study showed that adherence rates vary with different assessment methods. Some commonly used methods of treatment adherence, their advantages and disadvantages, practicality of application in India are discussed in Table II.

FACTORS AFFECTING ADHERENCE TO CML THERAPY

A variety of factors may affect treatment adherence. Patient-related factors include poor memory, forgetfulness, difference in perception levels and lack of understanding treatment instructions. In India high rates of illiteracy and poor education may affect cognitive levels and patients may not be able to fully comprehend instructions of drug usage or understand them wrongly. In the Ganesan *et al.* study, more than half the patients had poor understanding about the illness and planned treatment.¹⁹ Patients may hesitate to ask pertinent questions or seek more knowledge about the disease if a physician is unapproachable or less communicative. In India, treatment centres are busy and overcrowded; physicians may not be able to allocate sufficient time to patients to answer all their questions satisfactorily.

Non-adherence is also determined by patient attitudes. Some may lose motivation and discontinue treatment, some lack faith in benefits of complete treatment while some may get disillusioned with the side-effects. Younger patients may have lower adherence rates. In the report by Marin *et al.*, the median age for patients with an adherence rate $\leq 90\%$ was 43.8 years compared with 53.8 years for patients with adherence rate $>90\%$ ($p=0.004$).¹⁷ In another retrospective analysis, women were nearly twice as likely as men to have interruption in treatment ($p=0.009$).²⁰

A strong predictor for non-adherence is adverse events (AEs), which have been consistently implicated in illnesses requiring long-term treatment. AEs may range from minor inconveniences to debilitating conditions. The most commonly reported AEs (grades 1–2 severity) with imatinib are oedema, muscle cramps, diarrhoea, nausea, rash, fatigue and joint pains while more severe AEs (grades 3–4) include haematological events and elevated

TABLE II. Methods to measure adherence

Method	Description	Advantages	Disadvantages	Usage in clinical trials		Practicality of adopting in Indian setting
				Study	Adherence (%)	
Patient self-reporting	Patients are requested to recollect compliance which may be accomplished using patient diaries, treatment satisfaction/compliance questionnaires	<ul style="list-style-type: none"> • Simple, easy to administer • Cost-effective 	<ul style="list-style-type: none"> • Subjective • Propensity to over-report adherence • Influenced by recall bias 	Noens <i>et al.</i> (2009) (Basel Assessment of Adherence Scale) ¹³	64	Yes (however; questionnaires have to be translated into regional languages)
Pill counts	Count of unused pills returned by patients yields calculation of missed doses	<ul style="list-style-type: none"> • Simple, easy to administer • Cost-effective 	<ul style="list-style-type: none"> • Overestimates adherence (unused pills may be dumped) • Does not provide information about compliance with dosing schedule 	Noens <i>et al.</i> (2009) (ADAGIO) ¹³		Yes
Microelectronic monitoring system (MEMS)	An electronic device fitted into the medication bottle cap that records each time bottle is opened; a computerized list of dates and times of bottle openings for several weeks is obtained	<ul style="list-style-type: none"> • Good estimation of the number of doses taken and the dosing intervals 	<ul style="list-style-type: none"> • Act of opening a pill container does not guarantee consumption • Subject to bias (patient's awareness of the system itself) • Expensive 	Marin <i>et al.</i> (2010) ¹⁷ Ibrahim <i>et al.</i> (2011) ¹⁵	74 79	High costs prohibit use beyond a clinical research setting
Medication possession ratio based on pharmacy refill of prescriptions	Adherence is calculated as the amount of doses available to a subject in a given period, divided by the number of doses required for achieving full adherence during the same period of time	<ul style="list-style-type: none"> • Reliable estimation of actual drug use in large populations • Likely to identify treatment discontinuation • No recall bias and patient manipulation 	<ul style="list-style-type: none"> • No information about dosing interval and schedule • Doses may be missed, doubled but prescriptions still refilled on time 	Wu <i>et al.</i> (2010) ¹⁴ Ganesan <i>et al.</i> (2011) (patient visits for drug refills) ¹⁹	59 70	Yes
Blood sampling to measure drug levels	Serum drug levels used to estimate adherence	<ul style="list-style-type: none"> • Less biased estimation 	<ul style="list-style-type: none"> • Costly • Require additional centres in tissue/ blood sampling and laboratory testing • Subject to manipulation by taking extra doses or dosing just before test 			<ul style="list-style-type: none"> • Suitable in select those who can afford

liver enzymes. The comparison of nilotinib and imatinib as first-line therapy in the ENESTnd (Evaluating Nilotinib Efficacy and Safety in clinical Trials—newly diagnosed patients) study revealed lower rates of nausea, diarrhoea, vomiting, muscle spasm and oedema with nilotinib compared with imatinib while rates of rash, headache and alopecia were higher with nilotinib. Neutropenia was lower with nilotinib while thrombocytopenia and anaemia rates were comparable.²¹ Similarly, comparison of first-line therapy of dasatinib or imatinib in the DASISION (DASatinib versus Imatinib Study In treatment-Naive CML patients) study showed that non-haematological AEs were more frequent with imatinib than with dasatinib. Pleural effusion was seen in 10% of dasatinib-

treated patients and none in imatinib users.²² These AEs affect quality of life and often lead to intentional non-adherence where patients decide to miss doses to avoid experiencing AEs. In a study, patients with CML were asked to report current symptoms and their interference with daily activities. Of a total of 44 symptoms reported, most frequent were fatigue, pain and nausea. These symptoms interfered with daily activities in at least 30% of patients, leading some patients to stop or contemplate stopping treatment, or to decrease the dose/frequency of treatment.²³ Significantly lower adherence rates were reported by Marin *et al.* in patients with AEs such as asthenia, nausea, muscle cramps, bone or joint pains.¹⁷

Treatment complexities such as specific dietary restrictions and dosing requirements affect adherence. Once daily dosing (imatinib, dasatinib) offers an advantage over twice daily dosing (nilotinib). Nilotinib is affected by food and must be taken on an empty stomach, which requires patients not to eat for at least 2 hours before and 1 hour after taking the drug. In a survey on understanding the overall treatment burden and satisfaction among patients with CML, treatment difficulty was higher among users of nilotinib (63.3%) than imatinib (19.2%) and was least with dasatinib (2.6%) users ($p < 0.0001$). Nilotinib users reported more missed doses (mean [SD] 1.02 [1.60]) than imatinib users (0.45 [1.08]; $p < 0.05$).²⁴ The presence of comorbid conditions requiring other medications also affect adherence. In Darkow *et al.*'s analysis, adherence decreased as concomitant medications increased ($p = 0.002$) and treatment interruptions were more in patients with a high cancer complexity ($p = 0.03$).²⁰

Perhaps the biggest of all predictors of adherence are socioeconomic factors. In India, most patients cannot afford the high cost of treatment. In a typical middle class or a lower middle class family, patients may prefer family needs or responsibilities over their therapy. They may either discontinue treatment once they experience some clinical benefit or may restrict doses until they can manage sufficient funds to afford further therapy.

STRATEGIES TO ENHANCE ADHERENCE

Treatment adherence in chronic illnesses is a complex issue and is affected by many factors. Understanding the reasons for non-adherence in a patient helps decide what strategy works best for each individual and to provide tailored interventions.

Non-adherence due to patient attitude

Non-adherence due to patients' attitude is often difficult to change. Healthcare professionals play an important role in encouraging adherence. Improved patient-physician rapport, spending sufficient time with patients and caregivers explaining various aspects of the disease, educating them to recognize and immediately report AEs, prompt and appropriate management of the AEs help improve adherence.¹⁰ Importance of treatment adherence and how every single 'missed dose' may impact progress should be driven home. In overcrowded medical centres, clinicians often may not be able to allot sufficient time but it is worth remembering that a few extra minutes in the initial visits go a long way in saving time and healthcare costs due to potential negative clinical outcomes associated with non-adherence. An effective and economical solution would be to involve the healthcare team who could educate patients using flip charts, leaflets, audio/video messages in waiting areas or to set up special counters to provide adequate information to patients and clarify their doubts.

Unintentional non-adherence

Unintentional non-adherence due to forgetfulness can be overcome with support from family members who could successfully help incorporate medications into a patient's routine. Mobile phones are often used in interventions to increase adherence;¹¹ with the wide penetration of mobile phones in most remote villages, setting alarms or SMS for administration reminders helps in achieving better compliance.

Monitoring of response

Monitoring treatment response is important in CML. Unexplained increases in *BCR-ABL1* transcript levels, loss of response to treatment as determined by blood counts or cytogenetic testing, or

disease relapse marked by the manifestation of clinical symptoms are all signs of waning adherence and/or inadequate response to treatment. In Marin *et al.*'s series, 10/23 (44%) patients with unexplained increases had adherence rates $\leq 90\%$, whereas only 10/64 (16%) with no significant change in transcript levels had an adherence rate $\leq 90\%$ ($p = 0.01$).¹⁷ Timely monitoring helps identify decreased adherence allowing early interventions to improve adherence. The NCCN guidelines recommend molecular monitoring of *BCR-ABL1* transcript levels once every 3 months and evaluation for potential adherence problems when expected treatment response is not achieved at 3, 12 and 18 months. In India, there are few laboratories with facilities for molecular testing though some major cancer institutes are now trying to set up their own testing facilities.

Management of AEs

AEs of CML therapy may affect day-to-day activities and often lead to lowered adherence. Physicians and the healthcare team should reassure patients that AEs may be effectively managed and encourage patients not to stop taking their medication when AEs become uncomfortable. Physicians should proactively manage AEs. The NCCN guidelines provide specific recommendations for the management of AEs associated with TKIs. While AEs of grades 1–2 severity are often managed with supportive therapy, more severe AEs (grades 3–4) may require interruption of treatment followed by resumption at the original or reduced dose. Cytopenias are seen in a large number of patients on TKI therapy. Frequent monitoring of blood counts (weekly in the first month, monthly during the second and third months and every 3 months thereafter) is recommended. Patients should be educated to recognize related signs and symptoms (fever, infections and easy bruising) and report immediately. Peripheral oedema is another bothersome complication associated with TKIs. Treatment for moderate oedema includes close electrolyte monitoring, salt restriction, low-dose loop diuretics and potassium-magnesium supplements while severe oedema often necessitates treatment interruption.

Gastrointestinal (GI) AEs during TKI therapy include increased frequency of bowel movements in the initial treatment period but tend to return to normal after a few weeks. One way to tackle GI symptoms is to take TKIs with water and large meals (except nilotinib, which has to be taken in a fasting state). Some TKIs are associated with rare and serious AEs (nilotinib: peripheral arterial disease; dasatinib: pulmonary arterial hypertension), which may necessitate permanent discontinuation or switching to an alternative TKI. The NCCN guidelines provide detailed guidance on managing the AEs of TKI; in addition, individual prescribing information of each of these drugs should be referred for guidance.

Socioeconomic factors

Economic constraints may influence treatment decisions with patients often preferring family needs over their own. Non-adherence is associated with negative consequences which would mean a further financial burden; educating patients and caregivers about this possibility would help prioritize therapy above other needs.

Table III summarizes the factors affecting adherence and some mitigation strategies for non-adherence.

STOPPING IMATINIB: A REALISTIC GOAL?

Recently, researchers have been examining the possibility of discontinuing TKI therapy in select patients who achieve a stable molecular response. The Stop Imatinib (STIM) study was a

TABLE III. Factors affecting treatment adherence, and mitigation strategies

Category	Factors affecting adherence	Mitigation strategies
Disease factor	<ul style="list-style-type: none"> • Chronicity of the disease • Length of treatment 	<ul style="list-style-type: none"> • Continuous monitoring • Emphasis that missing even a few doses may lead to treatment failure
Patient factors	<ul style="list-style-type: none"> • Illiteracy • Patient perceptions • Level of cognition • Emotional factors such as depression 	<ul style="list-style-type: none"> • Patient counselling, continued motivation
Unintentional non-adherence	<ul style="list-style-type: none"> • Poor memory • Forgetfulness 	<ul style="list-style-type: none"> • Mobile phone reminders • Involving family members
Physician factors	<ul style="list-style-type: none"> • Busy and unapproachable physicians 	<ul style="list-style-type: none"> • Improved communication between patient and provider • Using flip charts, leaflets, audio/video messages or setting up of special information counters
Treatment-related factors	<ul style="list-style-type: none"> • Specific dietary restrictions • Complex dosing schedules 	<ul style="list-style-type: none"> • Offering simplified regimens to the extent possible • Encourage patients to adhere to preferred schedules
Drug side-effects	<ul style="list-style-type: none"> • Side-effects ranging from minor inconveniences to debilitating conditions may affect adherence 	<ul style="list-style-type: none"> • Proactive management of side-effects • Offer alternative therapies to patients who experience or are at risk for adverse events with a specific BCR-ABL inhibitor
Lack of treatment benefit	<ul style="list-style-type: none"> • Lack of improvement in the health condition may lead to demotivation, loss of faith and non-adherence 	<ul style="list-style-type: none"> • Continued counselling with frequent reinforcements • Monitor response and switch to alternative regimens if there is no response
Socioeconomic factors	<ul style="list-style-type: none"> • Economic constraints may influence treatment decisions 	<ul style="list-style-type: none"> • Educate patients to prioritize

prospective study to assess whether imatinib can be discontinued in patients with CMR. The results showed that in a subset of 69 patients with at least 12 months follow-up (median 24 months), molecular relapse occurred in 42 (61%) patients (40 before 6 months) though these patients responded to the reintroduction of imatinib (26 achieved CMR after imatinib rechallenge). Further, patients with imatinib therapy for at least 50 months had a 53% likelihood of molecular relapse, whereas this rate was 78% in patients with a shorter duration of treatment. Results of the STIM study were backed by similar evidence from the Australian TWISTER study. Persistence of CMR even after discontinuation in 41% (95% CI 29–52) of patients in the STIM study indicated the possibility of safely discontinuing imatinib in select patients. However, stopping imatinib is still not endorsed by international guidelines; currently, indefinite TKI therapy remains the preferred standard of care and discontinuation of therapy is only advised in the context of a clinical trial.^{25,26}

CONCLUSION

Although BCR-ABL TKIs have brought an unprecedented change in the outlook of patients with CML, monitoring and ensuring adherence to these agents is paramount in achieving optimal clinical benefits. Patient education, holistic healthcare approach encompassing drug therapy, behavioural counselling, improved patient-physician communication, early and aggressive management of AEs, strong family support and understanding are all strategies that may help to increase treatment adherence and help in optimizing TKI therapy.

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This monograph begins at the beginning—with a practical approach to a person with recently diagnosed diabetes, and then carries on systematically with a discussion on diet, physical activity, oral antihyperglycaemic agents and insulin. The latter half of the monograph covers the aspects of non-glycaemic management of diabetes, emphasizing that management of diabetes has to go beyond a glucocentric goal. This is followed by a discussion of the major microvascular complications of diabetes, namely retinopathy, nephropathy and neuropathy; and one of its most damaging complications—the ‘diabetic foot’.

**This book is an updated compilation of articles published in the
Everyday Practice section of the *Journal*.**

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