# Adherence to treatment with imatinib in chronic myeloid leukemia: a study of the first decade of responses obtained at a Brazilian hospital

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***Objective**: The aim of this study was to identify the reasons for failure in adherence to imatinib mesylate treatment in chronic myeloid leukemia.*

***Methods**: A retrospective review was performed of 100 non-electronic records of patients with Ph+ chronic myeloid leukemia treated with imatinib mesylate. The study period was from January 2001 to January 2011. Data were analyzed by Chi-Square and Correspondence analysis using the Statistical Analysis System software package.*

***Results**: At the beginning of treatment 41% of patients were in advanced stages of the disease. The unavailability of the drug (44.8%) and myelotoxicity (25.7%) were the most frequent reasons for interruption. The adherence rate was ≤ 90% in 47% of the cases. The low adherence influenced the cytogenetic response (p-value = 0.020) and molecular response (p-value = 0.001). Very high adherence (≥ 95%) induced complete cytogenetic response, major cytogenetic response and major molecular response.*

***Conclusion**: The population of this study obtained lower-than-expected therapeutic responses compared to other studies.*

***Keywords**: Leukemia, myelogenous, chronic, BCR-ABL positive/drug therapy; Piperazines/therapeutic use; Medication adherence; Fusion Proteins, bcr-abl/genetic; Treatment outcome*

## Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative syndrome characterized by the expansion of the clone of hematopoietic stem cells that carry the Philadelphia (Ph) chromosome[1]. The Ph chromosome results from the reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;11) with the formation of the BCR-ABL fusion gene which encodes a constitutively active protein – tyrosine kinase[1,2]. This translocation is found in 95% of CML patients[2]. Unregulated activity of this protein contributes to the malignant transformation of the disease by increasing granulocyte proliferation, decreasing apoptosis of leukemia cells, reducing cell regulation sensitivity by the bone marrow stroma, and promoting genetic instability[2]. The use of BCR-ABL tyrosine kinase inhibitors (TKIs), introduced more than a decade ago, revolutionized the treatment of CML. TKIs have changed the natural history of the disease in CML patients, who formerly had a prognosis of five or six years of life after diagnosis[3].

Various studies and several case reports have shown that the therapeutic response to imatinib mesylate (IM) treatment is directly associated to the plasma concentration of the drug[2,4-8]. One of the causes of decreased concentration of IM in the plasma is the lack of patient adherence to treatment; this directly influences the therapeutic response[4]. According to the World Health Organization (WHO), adherence is defined as the extent to which a person's behavior corresponds to the recommendations of a healthcare professional[9]. With regard to adherence in cancer patients, intravenous chemotherapy is correlated to a higher adherence rate because it occurs at a healthcare facility with the medication administered by an appropriate practitioner. As oral use involves the home environment and depends on the patients themselves, it tends to present a much lower adherence rate[10]. Ibrahim et al. demonstrated that lack of adherence was a factor that contributed to the loss of complete cytogenetic response in CML patients treated with IM[4].

The current study focused on the reasons that led to an interruption in the treatment protocol and the behavior of CML patients in respect to adherence to treatment over one decade of IM, correlating these aspects to the therapeutic responses attained.

## Methods

### Population

This is a retrospective and exploratory study. The study period was from January 2001 to January 2011. Participation in the study was limited to Ph chromosome positive CML patients

who had received treatment for no less than 12 months. Hence, from a population of 160 patients, 100 were eligible. As this is a ten-year survey, we will briefly mention the 60 patients who were excluded: 47 started IM treatment in advanced stages of the disease (37 in blast crisis and 10 in accelerated phase) and 13 in chronic phase. Regarding the outcome, 50 died, four abandoned treatment, four remain in treatment (newly diagnosed), one was transplanted, and one was lost to follow-up. The specialized outpatient clinic where the study was conducted, located in Fortaleza, the capital city of the state of Ceará, Brazil, treats patients from throughout that state. The outpatient clinic is part of Walter Cantídio University Hospital, of the Universidade Federal do Ceará. This study was approved (No. 040.04.11) by that institution's Ethics and Research Committee.

### Data

Data collection was from non-electronic patient charts, with all appropriate clinical records related to interruptions during the treatment period being tabulated for each patient, as well as observations of the continuation of the protocol through prescriptions. Data collection was conducted from June to August, 2011.

### Interruption of the Protocol

'Interruption' was considered as any occurrence of one or more days of non-use of the medication or any unauthorized change in dosage during the treatment of each patient.

To categorize patients as adherent or non-adherent, we used the concept of compliance (which in this context is synonymous to adherence), which expresses the percentage of dose taken versus dose prescribed[11]. This calculation was based on the MPR (Medication Possession Ratio) method, often adopted to evaluate compliance using, as a parameter, the days without medication that occur between intervals of replacement (or dispensation of the medication)[12].

In the present study, the result of compliance, expressed as a percentage, was obtained by adding the days of interruption and subtracted from the days of treatment for each case.

The classification into different ranges of compliance or adherence was based on those described in a pharmacoeconomic study by Darkow et al. about interruptions in IM treatment in CML patients where < 50% adherence was low, 50 to 90% was intermediate, 90 to 95% was considered high and > 95%, very high[13].

The reasons were defined as 'intentional' when the patient decided to change or discontinue treatment and 'unintentional' when the patient has the intention of taking the medicine, but is unable to do so[14].

The criteria for response to treatment follow the guidelines of the European LeukemiaNet, which defines the responses as follows: 1) complete hematologic response (CHR): normalization of total and differential white blood cell counts in peripheral blood and normalization of spleen size; 2) minimal cytogenetic response (minimal CyR): presence of 66-95% of $Ph^+$ metaphases; minor cytogenetic response (minor CyR): presence 36-65% of $Ph^+$ metaphases; partial cytogenetic response (PCyR): presence of 1-35% $Ph^+$ metaphases; complete cytogenetic response (CCyR): 0% $Ph^+$ metaphases; major cytogenetic response (major CyR): PCyR plus CCyR; 3) molecular response (MR): ≥ 3 log reduction in the BCR-ABL transcripts; major molecular response (Major MR): reverse transcription polymerase chain reaction (RT-PCR) negative and complete molecular response (CMR) negative[15].

### Statistical Analysis

The data were analyzed using the Statistical Analysis System software package employing the following techniques: Chi-Square and Correspondence analysis. Values were considered significant when the p-value < 0.05 with a 95% confidence interval (95% CI).

## Results

### Population

This study involved 100 patients. The median age of the population at the time of diagnosis was 44.5 years

Table 1 - Study population profile

| Characteristics | |
|---|---|
| **Age at diagnosis - median (range)** | 44.5 (13-77) |
| **Gender - %** | |
| Male | 50 |
| Female | 50 |
| **Stage of disease at diagnosis - %** | |
| Chronic | 96 |
| Accelerated | 2 |
| Blast crisis | 2 |
| **Stage of the disease at start of treatment with IM - %** | |
| Chronic | 59 |
| Accelerated | 28 |
| Blast crisis | 13 |
| **Treatment prior to IM - %** | |
| Hydroxyurea (hydroxycarbamide) | 28 |
| Busulfan and hydroxyurea | 2 |
| Busulfan, hydroxyurea and interferon | 3 |
| Hydroxyurea and interferon | 58 |
| Hydroxyurea and anagrelide | 1 |
| Busulfan, hydroxyurea, interferon and allogeneic BMT | 1 |
| Hydroxyurea and Relapsed ALL Protocol - 1996 | 1 |
| Hydroxyurea and allogeneic BMT | 2 |
| Interferon | 1 |
| No record | 2 |
| **Initial dose of IM - %** | |
| 300 | 1 |
| 400 | 78 |
| 600 | 21 |
| **Distance between patient's home and outpatient clinic - %** | |
| < 100 km | 66 |
| 101 - 200 km | 14 |
| 201 - 300 km | 8 |
| 301 - 400 km | 7 |
| 401 - 500 km | 3 |
| > 501 km | 2 |

IM: imatinib mesylate; BMT: Bone marrow transplantation

(range: 13-77) with equal distribution by gender. Most (96%) of the population were in the chronic phase at diagnosis. The association of hydroxyurea with interferon (58%) followed by monotherapy with hydroxyurea (28%) was the most common treatment prior to IM. Despite the very high prevalence of the chronic phase at diagnosis, at the start of treatment with IM only, 59% of the patients were in chronic phase, 28% were in the accelerated phase and 13% in blast phase (Table 1). The initial dose for most of the population (78%) was 400 mg/day. Regarding the geographical location of the patient's home, 66% lived within 100 km of the outpatient clinic, however, there were cases where this distance was greater than 500 km.

### Reasons of Interruption

The results show that in this population there was a predominance of unintentional interruption compared to intentional causes. The unavailability of the product in the healthcare service was the most prevalent (44.8%) of all causes. The main hematologic reactions observed were thrombocytopenia (9.4%) and thrombocytopenia with leukopenia (8.1%) grades 3 and 4. As for gastrointestinal tract (GIT) intolerance, reactions such as diarrhea, nausea, vomiting, and abdominal pain represented 3.6% of the cases. Non-hematologic and non-GIT reactions occurred in 7.4% of cases, mainly due to drug eruption (rash) and edema. Of the intentional causes, missing an appointment and taking a lower-than-prescribed dose were equally reported (2.5% - Table 2).

### Adherence versus response

On analyzing Table 3, one can see that, in this first decade of the use of IM at the institution, 47% of the population adhered to treatment (≤ 90%).

No correlation was found between adherence and the distance between the patient's home and the clinic (p-value = 0.890), gender (p-value = 0.595) and age (p-value = 0.942). All of the categories that presented frequency ≤ 5% were grouped. Thus, we found that cytogenetic and molecular responses were dependent on adherence.

Figure 1A demonstrates that CCyR is associated with very high adherence. Major CyR, Minor CyR and Minimal CyR are related to high adherence, while Absent CyR is related to lower adherence. Regarding MR, patients with very high adherence attained Complete MR and Major MR, however high adherence did not induce MR (Figure 1B). Intermediate adherence was prevalent in individuals who did not exhibit MR.

### Outcomes

At the end of the study, 5% of the patients had abandoned treatment, 68% continued treatment on drugs, 23% had died, 3% had been transplanted and 1% was lost to follow-up. Of the patients on drug treatment, 35% continued taking IM, 17% were taking dasatinib, 10% were taking nilotinib, 4% were taking hydroxycarbamide (hydroxyurea), and 2% were in expectant management.

Table 2 - Interruptions in treatment

| Reasons for interruption | | | |
|---|---|---|---|
| **Unintentional** | **RF (%)** | **Intentional** | **RF (%)** |
| Unavailability of medication at healthcare service | 44.8 | Missed appointment | 2.5 |
| Suspension due to thrombocytopenia | 9.4 | Took less than the prescribed dose | 2.5 |
| Suspension due to thrombocytopenia and leukopenia | 8.1 | Interruption due to social events | 1.1 |
| Adverse reaction (except hematologic and GIT) | 7.4 | Abandonment | 0.7 |
| Suspension due to leukopenia | 5.1 | Suspension due to pregnancy or suspected pregnancy | 0.7 |
| Intolerance of GIT | 3.6 | Took more than the prescribed dose | 0.4 |
| Forgot | 3.3 | Stopped taking the medication because symptoms improved | 0.2 |
| Suspension due to thrombocytopenia, leukopenia and anemia | 1.8 | | |
| Complication from other pathology(ies); Suspended by physician at specialized healthcare service | 1.6 | | |
| Complication from other pathology(ies); Suspended by physician at other healthcare service | 1.3 | | |
| Complication from other pathology(ies); Suspended by the patient | 1.3 | | |
| Other | 1.3 | | |
| Dependence on third parties | 1.1 | | |
| Suspension due to anemia | 1.1 | | |
| Financial difficulties | 0.5 | | |
| Suspension due to thrombocytosis | 0.2 | | |

RF: Relative Frequency

Table 3 - Adherence versus response

| Responses \ Adherence | Intermediate 50-90% (n = 47) | High 90-95% (n = 22) | Very high > 95% ( n = 31) | Total (n = 100) |
|---|---|---|---|---|
| **Hematologic response (p-value = 0.826)** | | | | |
| Complete hematologic response | 43 | 21 | 29 | 93 |
| Partial hematologic response | 2 | - | 2 | 4 |
| Absent hematologic response | 1 | 1 | - | 2 |
| **Cytogenetic response (p-value = 0.020)** | | | | |
| Complete cytogenetic response | 11 | 9 | 18 | 38 |
| Major cytogenetic response | 4 | 4 | 1 | 9 |
| Minor cytogenetic response | 2 | 2 | - | 4 |
| Minimal cytogenetic response | 2 | - | 1 | 3 |
| Absent cytogenetic response | 13 | 6 | 8 | 27 |
| **Molecular response (p-value = 0.001)** | | | | |
| Complete molecular response | 1 | 2 | 5 | 8 |
| Major molecular response | 5 | 5 | 13 | 23 |
| Absent molecular response | 17 | 11 | 6 | 34 |

FR: Relative Frequency; GIT: gastrointestinal tract

Note: The table shows consolidated responses, except for those that did not include exams: CBC (n = 1), cytogenetics (n = 20), and molecular (n = 36)

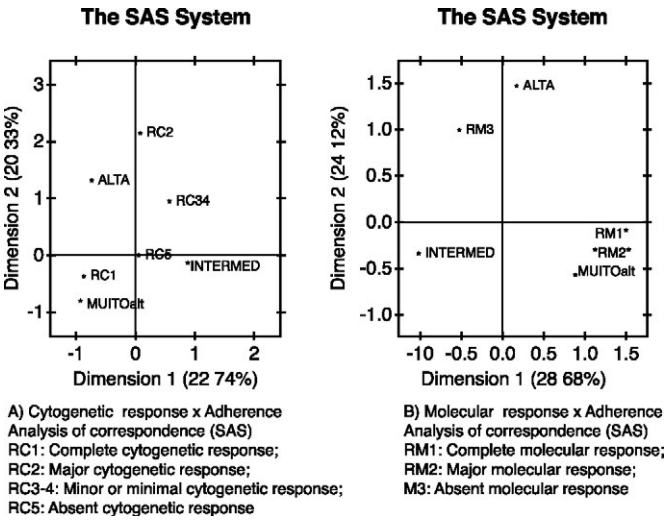


Figure 1 – Cytogenetic and molecular response versus Adherence

## Discussion

After over a decade from the introduction of IM to treat CML, several studies have sought to analyze adherence to (or compliance with) the drug therapy. These studies used different sample sizes and primarily indirect methods to measure and classify patients' adherence, conferring limitations that may suggest bias, such as falsehoods stated by patients during interviews. Therefore, these considerations should be taken into account when analyzing the results of our study.

As seen in Table 3, 47% of the cases were classified as having adherence below the ideal (≤ 90%); other studies reported this percentage as below 35% (Table 4). A study conducted on 267 patients published by Darkow et al. argued that the lack of adherence was significantly higher in women; in the present study this difference was not observed (p-value = 0.595)[13]. Another adherence study of 87 patients by Marin et al. showed that adherence was lower in younger patients, unlike our results, in which age did not influence adherence (p-value = 0.942)[16].

Table 4 - Summary of studies on adherence to imatinib mesylate treatment in chronic myeloid leukemia

| Study | Method used | Non-adherence rate (%) | Consequence of non-adherence |
|---|---|---|---|
| Noens et al.[19] | Questionnaire and pill count | 32.7 | Increased risk of suboptimal responses |
| Marin et al.[16] | Electronic monitoring device | 26 | Reduced possibility of achieving major and complete molecular response |
| Darkow et al.[13] | Electronic data on dispensation | 31 | Increased healthcare costs |
| Ganesan et al.[17] | Patient's return for dispensation | 29 | Reduced event-free survival |
| Present study | Data from non-electronic medical records | 47 | Reduced possibility to achieve and maintain hematologic, cytogenetic and molecular response |

Adapted from Ganesan et al. (2011)[17]

Our findings demonstrate that, as a consequence of non-adherence, the patients had lower clinical results than those observed in other studies, particularly in relation to CyR and MR. The update of the International Randomized Study of Interferon and STI-571 (IRIS) showed the possibility of 98% of patients achieving CHR, 87% CCyR and 80% Major MR, all being treated with a daily dose of 400 mg in chronic phase CML[1]. The study by Lavallade et al. in 204 patients obtained a CHR rate of 98.5%, while the rates of CCyR and major MR were lower than the IRIS: 82.7% and 50.1%, respectively[18]. In the present study population, only 59% of the patients began treatment in the chronic phase of the disease with 38% and 23% of the cases attaining Major MR and CCyR, respectively. Marin et al. found that patients with adherence ≤ 80% and ≤ 90% did not obtain Major MR and CMR, respectively. In our findings, adherence ≤ 95% is related to Absent MR[16]; however, the CHR achieved by 97% of patients is similar to that found by Noens et al. in the Adherence Assessment with Glivec: Indicators and Outcomes study (ADAGIO study). These data suggest that, at some point, our population suffered interruptions in treatment that led to failure to attain or to loss of CyR and MR[4,19]. Another factor that may have contributed to the low consolidated MR is the lack of an examination to quantify BCR-ABL.

The identified reasons that lead to non-adherence to treatment by the study population are similar to those described by Eliasson et al., who explored the reasons leading to interruption of treatment. However, those researchers found that, during treatment, the unintentional reasons tend to decrease while intentional reasons follow the opposite trend, precisely because patients respond well to the treatment[14]. In our population, between 2006 and 2011, the most frequent reason was the unavailability of the drug at the healthcare service; this was the predominant factor in non-intentional interruption by the patient.

In Brazil, IM has been distributed through the Brazilian National Health Service (SUS) since 2001[20]. However, at that time, under the Clinical Protocols and Therapeutic Guidelines (PCDT) adopted by the SUS, IM was prescribed as a first-line treatment for patients in accelerated phase or blast crisis and as a second-line treatment for patients in chronic phase who are interferon intolerant. Only in 2008[21] did IM become the first-line treatment for chronic phase CML, with a resulting increase in patient demand for the service. These factors impacted on the supply of IM at our clinic, which budgeted in the entire study period a sum of nearly R$ 15,500,000.00 for this drug. Therefore, based on the SUS's principle of equality, since 2008 it has been determined that the supply of IM should meet the needs of all patients, so 15-day quantities are being supplied, i.e., the patient must return every 15 days to receive the medication. Even so, the results show that there is no relationship between adherence and distance from the patients' homes to the outpatient clinic (p-value = 0.890).

Among the most frequent side effects with the use of IM is myelosuppression with neutropenia and/or thrombocytopenia, especially in the later stages of the disease[22]. Thus, it is evident that the late start of treatment contributed to a high frequency (25.7%) in the suspension of the medication among the study population, suggesting an increase in public spending on healthcare and loss of control of the disease[13].

Through the SAS/MS Ordinance 90 of March 16, 2011[23], the Ministry of Health centralized and directly took over the purchase of IM in Brazil, distributing it through the Health Departments in each state. Thus, we hope that this measure will assure the availability of the drug, guaranteeing continuity of treatment for not only long-term patients but also newly diagnosed patients. Note that this measure assures access to the drug, but it is necessary to further improve access to laboratory tests for monitoring the therapeutic response, such as the quantitative Polymerase Chain Reaction (PCR) for BCR-ABL[24]. As shown in Table 3, cytogenetics and PCR tests were not performed in 20% and 36% of the population, respectively.

Analyzing the reasons for unintentional interruptions (8.1%), it becomes evident that there is a need for a multidisciplinary team, which will help to understand the diagnosis, acceptance of treatment and relief of side effects, in addition to favoring closer practitioner-patient relationships. As an example of the importance of the role of the multidisciplinary team, we highlight a Korean study of 114 patients divided into two groups (50:50). One group was assisted by a 'Care Club' and the other one was not. The 'Care Club' was made up of healthcare professionals offering counseling on adverse reactions, clinical follow-up exams, and a telephone number was available for patients to call and clarify doubts. As a result, the club was effective in the persistence of treatment, resulting in improved overall adherence (93.0 ± 2.3%) when compared to patients who were not part of the club (76.2 ± 7.4%)[24].

According to Ruddy et al., simple actions such as informing the patient about the characteristics of the disease, the risks and benefits of treatment, access to consultations with the pharmacist and a focus on correct use of the medication can improve adherence[25].

The treatment of CML is an example of a therapeutic revolution achieved through the relentless pursuit of a cure for malignant diseases, whereby, in addition to improving the life quality of patients, there has been a change in the natural history of the disease, allowing an increase in survival after diagnosis. But the conditions imposed by Brazil's national healthcare policies and the manner in which the drug was distributed at our clinic during this first decade of treatment reduced the potential benefits.

At a time in which only patients who were at an advanced stage of the disease or who were interferon intolerant could be included, the period that elapsed between diagnosis and the use of IM was prolonged, clearly indicating the need for a broader discussion, a more effective participation of healthcare professionals at the time of public consultations, and earlier updating of the clinical protocols and therapeutic guidelines in the Brazilian SUS. Furthermore, values calculated for transfer of funds from the SUS to partner institutions should cover not only the medication, but also clinical and laboratory exams to evaluate and monitor the patient's clinical evolution.

## Conclusion

In this first decade of CML treatment with IM, the outpatient clinic described in this paper had results that fell short of those described in the literature. However, with the improvements already made in relation to the acquisition of the drug, a successful future in favor of the health and life quality of patients with CML is awaited.

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