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Association between the profile of patients with chronic myeloid leukemia and adherence to tyrosine kinase inhibitors

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Abstract

Background: Tyrosine kinase inhibitors have substantially improved the quality of life and survival of patients with chronic myeloid leukemia. However, adherence is a complex and crucial aspect for achieving the desired clinical outcomes. Various factors can influence adherence, including the knowledge about the medications used in treatment.
Aim: To investigate the association between the clinical, sociodemographic and pharmacotherapeutic profile of patients with chronic myeloid leukemia and adherence to tyrosine kinase inhibitors.
Method: This is a cross-sectional study conducted in a specialized outpatient clinic for hematological diseases in the Central-West region of Brazil. Treatment adherence was assessed using the Morisky medication adherence scale and the medication possession ratio. A binary logistic regression was performed to investigate the extent to which adherence could be adequately predicted by the independent variables.
Results: The study included 153 patients, with a mean age of 51.8 years and a predominance of males (59.5%). Low adherence was observed in 56.2% of patients (Morisky scale) and 24.8% (medication possession ratio). Among the predictors, being male increased the chances of low adherence by 2.22 times and having comorbidities by 2.17 times. Conversely, an increase in diagnosis time was associated with a 0,09 decrease in the chances of low adherence and "Knowing what to do if you miss a dose" was associated with a 0,58 lower chance of low adherence.
Conclusion: Our study emphasized that adherence can vary depending on the method used and that predictors related to clinical, sociodemographic and pharmacotherapeutic characteristics may be associated with low adherence.

Keywords

Medication adherence, tyrosine kinase inhibitors, chronic myeloid leukemia, knowledge

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Impact statements

Adherence to tyrosine kinase inhibitors (TKI) is a crucial factor in achieving the desired clinical outcomes in chronic myeloid leukemia (CML).

Identifying the factors that influence adherence provides valuable insights to healthcare professionals involved in patient care and aids in developing specific strategies targeted at predictors that potentially influence low adherence.

Improving adherence can enhance pharmacotherapeutic outcomes and, consequently, survival rates, while also reducing costs associated with hospitalizations and medication changes.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that affects the myeloid cells of the bone marrow.[1] The incidence of CML is 1 to 2 new cases per 100,000 inhabitants per year, accounting for approximately 15% of all adult leukemia cases.[2] When untreated or if the patient does not achieve an adequate response to treatment, CML progresses from a chronic phase to an accelerated transformation phase, ultimately culminating in the acute blast phase, which is the terminal stage of the disease.[1]

In recent years, targeted molecular therapy has positively impacted the outcomes of onco-hematological patients.[3] Imatinib, the first specific tyrosine kinase inhibitor (TKI) approved for the treatment of CML, marked a significant advancement in the management of the disease. With the increase in resistance, second and third generation TKI were developed.[1] The introduction of these medications has brought the life expectancy of patients closer to that of the general population and has turned CML into a manageable chronic condition through appropriate continuous treatment.[4] However, treatment adherence remains one of the greatest challenges for achieving maximum pharmacotherapy effectiveness.[5]

Patients with CML who demonstrate high adherence to treatment have significantly better five-year overall survival rates (97.2%) compared to those with low adherence (70.2%).[6] However, nearly half of the patients face challenges with adherence to TKI treatment.[7] In patients using imatinib, adherence has been shown to be a predictor of loss of cytogenetic response and therapeutic failure.[8] Additionally, in patients with CML, non-adherence to TKI contributes to more frequent hospitalizations and additional healthcare costs.[9]

Poor adherence to the treatment of chronic diseases, such as CML, is a multifactorial problem, and patient characteristics can influence it.[10]

Although studies consistently demonstrate that adherence to imatinib is low (15.3%–43%),[7,11] and that 26% of patients using nilotinib and 19% using dasatinib were considered non-adherent,[12] few have investigated the relationship between demographic and clinical factors and adherence.[11–14] Furthermore, two of these studies evaluated only newly diagnosed patients.[11,12] The literature on adherence has been limited to assessing adherence by only one method,[11–14] and the only study that used two methods did not investigate associated factors. Studies that examined patient knowledge regarding TKIs[14,15] did not analyze this relationship using logistic regression techniques. Moreover, no study has yet evaluated the influence of pharmacotherapy complexity on adherence. Considering that CML is a chronic disease manageable with pharmacological treatment,[4] understanding the factors that influence adherence is necessary, as this can contribute to improved health outcomes, reduced need for medication changes due to therapeutic failure and decreased hospitalizations due to disease complications.[9]

Aim of the study

To investigate the association between clinical, sociodemographic and pharmacotherapeutic profile of patient with CML and adherence to ITK.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee under protocol number 14964619.1.0000 .5078.

Method

Study design and population

This is a cross-sectional study conducted in a specialized outpatient clinic for the care of patients with onco-hematological diseases, at a large university hospital in the Central-West region of Brazil.

Data collection

Patients with CML aged 18 years or older who were seen at the outpatient clinic between November 2019 and May 2023 were included in the study. Exclusion criteria were patients on third-line treatment (due to limited access to some data), those without cognitive or clinical conditions to participate in the study (such as hearing, visual, or speech impairments), and pregnant women.

In Brazil, the first line of treatment for CML is carried out with imatinib, and in cases of resistance or intolerance, the second line of treatment (nilotinib or dasatinib) is used. These medications are provided by the Unified Health System (SUS) at no financial cost to the patient and were dispensed at the same hospital where the study was conducted. However, if the third line of treatment was required, it was obtained through SUS-authorized hospitals, such as High-Complexity Oncology Care Units (or High-Complexity Oncology Care Centers.[16]

The sample size was calculated using the method for finite populations[17] followed by stratified sampling based on the TKI in use. A list containing the patients' medical records was provided, and the patients to be included in the study were randomly selected using the website www.sorteador.com.br. If a selected patient did not meet the inclusion criteria or was no longer in treatment at the outpatient clinic, a new selection was made. Interviews were conducted on the day of the medical consultation at the hematology outpatient clinic. The data collection form was calibrated with ten patients who were not included in

the final sample, and data were collected by a team of trained researchers. The data were entered into a database created in Research Electronic Data Capture (REDCap).

Variables

Sociodemographic variables: gender, age, marital status, education level, birthplace, occupation, income. Clinical variables: comorbidities, time since CML diagnosis, BCR-ABL result, molecular response.[18] Pharmacotherapeutic variables: TKI in use, number of medications in use (polypharmacy),[19] pharmacotherapy complexity index,[20] knowledge about the TKI in use.[21] Adherence was estimated using the Morisky Test: High degree of adherence and low adherence (intentional, unintentional and both behaviors[22] and Medication Possession Ratio (MPR) the patients were considered to be adherent when the MPR was $\geq 90\%$.[5]

Statistical analysis

Numerical variables were analyzed using measures of central tendency (mean, median and standard deviation), and categorical variables were analyzed using relative and absolute frequencies. Numerical variables (age, number of medications in use, pharmacotherapy complexity index, knowledge about medications in use, and MPR) were tested for normality using the Shapiro-Wilk test.

Bootstrap procedures were performed (2000 re-samplings; 95% BCa CI) to increase the reliability of the results, correct deviations from normality in the sample distribution, address differences between group sizes, and to present a 95% confidence interval for the mean differences.[23]

The association of categorical variables was tested using Pearson's chi-squared test or Fisher's exact test. The difference between the means of numerical variables was tested using Student's t-test with a significance level of 5%. Effect sizes were determined by calculating Cohen's d and Crame's v coefficients for variables with statistically significant results ($p < 0.05$).

A binary logistic regression was conducted to investigate the extent to which adherence assessed by the Morisky test (high adherence and low adherence) could be adequately predicted by sociodemographic and clinical variables. The "stepwise backward" selection method was used in logistic regression, starting with all candidates independent variables and gradually removing those that did not significantly contribute to the model based on minimizing the Akaike Information Criterion(AIC). Additionally, multicollinearity among variables included in the model was tested using the Variance Inflation Factor (VIF), with VIFs less than five suggesting independence between variables, thus enhancing the reliability of logistic regression results.[24] Analyses were conducted with a significance level of 5% and a confidence level of 95%. The analyses were performed using R software version 4.2.3.

Results

The study included 153 patients. Concerning sociodemographic characteristics, the mean age was 51.8 years (SD = 14.4), with a median of 52.0 years (range from 18 to 83). There was a predominance of male patients, accounting for 59.5% (n = 91). About clinical characteristics, the mean time since CML diagnosis was 9.1 years (SD = 5.6), with 61 patients (39.9%) presenting at least one comorbidity in addition to CML. The pharmacotherapy complexity had an average of 6.79 (SD = 5.3) (range from 2 to 23.5) (Table 1).

In respect of adherence metrics, low adherence was observed in 86 (56.2%) of the patients assessed by the Morisky test and in 38 (24.8%) of the patients assessed by the MPR (Table 1).

Regarding patient knowledge about TKI, 31 (20.3%) did not know the duration of CML treatment, and 35 (22.8%) did not know what to do if they missed a dose of medication. Additionally, almost half of the patients, 66 (43.1%), were unable to report medications, foods, or beverages that interacted with TKI. In the overall knowledge score, 29 (19.0%) of the patients had regular or insufficient knowledge (Table 1).

Knowing what to do in case of forgetting to take medication ($p = 0.033$; Cramer's v = 0.16) and time since diagnosis ($p = 0.035$; Cohen's d = 0.33) showed a statistically significant association with low adherence. Pharmacotherapy complexity ($p = 0.088$), presence of comorbidities ($p = 0.096$), and knowledge about TKIs ($p = 0.070$) showed a significant trend of association with low adherence (Table 2).

The AIC of the initial logistic regression model was 209.18, while the selected final model resulted in an AIC of 190.18. Considering the analysis of multicollinearity, all variables included in the regression model had VIF <2, except for occupation with VIF = 3. The final binary logistic regression model was statistically significant ($\chi^2 = 43.65$, $p = 0.02$, Nagelkerke $R^2 = 0.35$). Among the predictors, being male increased the odds of low adherence by 2.2 times and having at least one comorbidity besides CML increased the odds by 2.17 times. Conversely, each additional year since diagnosis was associated with a 0,09 decrease in the odds of low adherence. Although marginally significant, knowledge about "what to do if a dose is missed" was associated with 0,58 lower odds of low adherence (Table 3).

Discusssion

Our study analyzed the profile of patients with CML to identify predictors of adherence to TKIs in patients undergoing different treatment regimens. Our findings indicated differences between the results of the adherence metrics used. It was observed that most patients demonstrated low

Table 1. Sociodemographic and clinical characteristics of patients with CML treated at a hematology outpatient clinic in Goiás (n = 153).

Characteristics	Number (%)
Age	51.8 (14.4)[a]
Gender	
Male	91 (59.5%)
Female	62 (40.5%)
Marital status	
With partner	94 (61.4%)
No partner	59 (38.6%)
Education	
Elementary School	72 (47.1%)
High school	51 (33.3%)
Graduated	23 (15.0%)
Illiterate	7 (4.6%)
Occupation	
Retiree	51 (33.3%)
Worker with employment contract	43 (28.1%)
Freelancer	32 (20.9%)
Housewife	18 (11.8%)
Unemployed	9 (5.9%)
Family income	
Up to 1.5	73 (47.7%)
1.51 to 3	46 (30.0%)
Above 3	31 (20.3%)
Not informed/Unknown	3 (2.0%)
Birthplace	
Outside of Goiânia	119 (77.8%)
Goiânia	34 (22.2%)
Comorbidities	
No	92 (60.1%)
Yes	61 (39.9%)
Time of diagnosis	9.1 (5.6)[a]
Unknown	1
Polypharmacy[b]	
No	123 (80.4%)
Yes	30 (19.6%)
Complexity of pharmacotherapy	6,79 (5.3)[a]
BCR-ABL International Scale	
≤0,1%	53 (34.8%)
Undetectable	33 (21.7%)
≤0,01	25 (16.5%)
≤a 0,0032%	21 (13.8%)
≤1%	12 (7.9%)
≤10%	7 (4.61)
100%	1 (0.6%)
Unknown	1 (0.6%)
ITQ	
Imatinib	102 (66.7%)
Dasatinib	26 (17%)
Nilotinib	25 (16.3%)
Adherence	
Morisky	
Unintentional low adherence	68 (44.4%)
High degree of adherence	67 (43.8%)
Intentional low adherence	10 (6.5%)
Low adherence with both behaviors	8 (5.2%)
MPR	
≤90%	38 (24.8%)
≥90%	115 (75.2%)
Knowledge about the ITQ	
Know the name	
Yes	143 (93.5%)
No	10 (5.5%)
Know the indication of the medicine	
Yes	146 (95.4%)
No	7 (4.6%)
Know the dose of the medicine	
Yes	141 (92.2%)
No	12 (7.8%)
Know when to take the medicine	
Yes	152 (99.3%)
No	1 (0.7%)
Know the treatment time	
Yes	122 (79.7%)
No	31 (20.3%)
Know how to use the medicine	
Yes	146 (95.4%)
No	7 (4.6%)
Know what to do if forget to take the medicine	
Yes	118 (77.1%)
No	35 (22.8%)
Medicine or food or drink that you should avoid	
Yes	87 (56.9%)
No	66 (43.1%)
Know if the medicine can cause adverse reactions	
Yes	129 (84.3%)
No	24 (15.7%)
Had adverse reactions	
Yes	119 (77.8%)
No	34 (22.2%)
Calculation Knowledge about the ITQ	
Good	124 (81.0%)
Regular	23 (15.0%)
Insufficient	6 (4.0%)

[a]Mean (standard derivation)
[b]Polypharmacy: Five or more drugs.[19]

adherence to treatment according to the Morisky test, and that adherence can be influenced by clinical and sociodemographic characteristics, such as gender, comorbidities, time since diagnosis, and knowing what to do if a dose is missed.

Concerning sociodemographic characteristics, our results were like those of other studies. In a study conducted in the northern region of Brazil, there was a predominance of males at 60% (n = 153) and a mean age of 50 years.[14] Another study conducted in China also identified a predominance of males at 56.5% (n = 398) and a median age of 43 years.[25] Understanding the sociodemographic profile

Table 2. Association between sociodemographic and clinical variables and adherence assessed by the Morisky test (n = 153).

Variables	Low adherence Morisky test	*p*-value	*p*-value bootstrapping	95% C.I	Effect
Age*	50.3 (13.5)	0.152	0.149	−1.15–7.99	–
Gender***		0.187	–	0.31–1.28	–
Male	47 (51.6%)				
Female	39 (62.9%)				
Marital status **		0.372	0.474	0.00–7.68	
With partner	56 (59.6%)				
No partner	30 (50.8%)				
Education**		0.115	–	0.15–12.59	–
Elementary School	42 (58.3%)				
High school	28 (54.9%)				
Graduated	15 (65.2%)				
Illiterate	1 (14.3%)				
Birthplace**		0.350	0.492	0.00–7.98	–
Outside of Goiânia	64 (53.8%)				
Goiânia	22 (64.7%)				
Occupation**		0.106	0.285	0.34–15.37	–
Retiree	24 (47.1%)				
Worker with employment contract	25 (58.1%)				
Freelancer	20 (62.5%)				
Housewife	14 (77.8%)				
Unemployed	3 (33.3%)				
Family income**		0.161	–	1.25–14.80	–
Up to 1.5	37 (50.7%)				
1.51 to 3	25 (54.4%)				
Above 3	22 (70.9%)				
Not informed	2 (100.0%)				
Time of diagnosis*	9.9 (6.1)	0.035	0.035	−3.56–(−0.16)	0.33[a]
Multimorbidities ***		0.096	–	0.27–1.12	–
No		57 (37.2)			
Yes		29 (18.9)			
Molecular Response**		0.518	0.368	0.00–6.36	–
Yes	75 (49.0%)				
No	11 (55.0%)				
ITQ**		0.652	0.234	0.0–3.47	–
Imatinibe	55 (53.9%)				
Nilotinibe	15 (57.7%)				
Dasatinibe	16 (64.0%)				
Polypharmacy**		0.332	0.500	0.00–8.03	–
No	72 (58.5%)				
Yes	14 (46.7%)				
Complexity of pharmacotherapy*	6.2 (4.6)	0.119	0,088	−0.30–3.17	
Unknown	2				
Name of the medice***		0.105	–	0.69–19.97	–
Yes	83 (58.0%)				
No	3 (30.0%)				
Know the indication of the medicine**		0.699	–	0.258–12.37	–
Yes	83 (56.8%)				
No	3 (42.9%)				
Know the dose of the medicine***		0.367	–	0.49–7.90	–
Yes	81 (57.4%)				
No	5 (41.6%)				
Know when to take the medicine**		>0.999	–	–	–
Yes	85 (55.9%)				
No	1 (100.0%)				

(continued)

Table 2. Continued.

Variables	Low adherence Morisky test	*p*-value	*p*-value bootstrapping	95% C.I	Effect
Know the treatment time***		>0.999	–	0.44–2.55	–
Yes	69 (56.56%)				
No	17 (54.84%)				
Know how to use the medicine***		0.468	–	0.04–3.17	–
Yes	81 (55.5%)				
No	5 (71.4%)				
Know what to do if forget to take the medicine***		0.033	–	1.02–5.50	0,16[b]
Yes	72 (61.0%)				
No	14 (40.0%)				
Medicine or food or drink that you should avoid**		0.192	–	0.78–3.13	–
Yes	53 (60.9%)				
No	33 (50.0%)				
Know if the medicine can cause adverse reactions**		0.273	–	0.62–4.37	–
Yes	75 (58.1%)				
No	11 (45.8%)				
Had adverse reactions**		0.558	–	0.31–1.73	–
Yes	65 (54.6%)				
No	21 (61.7%)				
Need more information**		0.605	–	0.47–5.19	–
No	75 (55.1%)				
Yes	11 (64.7%)				
Knowledge about the ITQ**		0.070	–	–	
Good	74 (59.7%)				
Regular	11 (47.8%)				
Insufficient	1 (16.7%)				
Resultado BCR/ABL*		0.319	0.163	–0.24–9.82	–

* Student's t-test; **Pearson's Chi-squared test; ***Fisher's Exact Test
[a]Cohen d.
[b]Cramer v
Molecular Response: ⩾3-log reduction[18]

Table 3. Predictive variables of low adherence according to the Morisky test.

Variable	Wald	Df[a]	Sig[b]	Exp(B)[c]	95% C.I.for EXP(B)	
					Lower Limit	Upper Limit
Male gender	4,21	1	0,03	2,22	1,05	4,84
Comorbidity	4,07	1	0,04	2,17	1,03	4,71
Time since diagnosis	6,45	1	0,008	0,91	0,85	0,97
Knows what to do if a dose is missed	4,29	1	0,05	0,42	0,17	1,0
Constant	0,41	1	0.000	0.000	–	–

[a]Degrees of freedom.
[b]Significance.
[c]Odds ratio.

can guide the development of specific educational and support strategies for these patients, with the aim of improving treatment adherence and clinical outcomes.

Regarding adherence metrics, despite the divergence between the methods used, our findings are consistent with the literature. Results from a study conducted in Tanzania showed that nearly half of the patients had low adherence according to the Morisky test.[7] Another study conducted in Malaysia, using the MPR, revealed that the non-adherence rate to imatinib was approximately one-quarter.[13] These findings can be partially explained by the fact that even if patients regularly obtain their medication, they may not use it properly. This is because the MPR is an estimate of primary adherence, based on medication

dispensing, and one of its limitations is its insensitivity to changes in patient behavior over time.[26] Therefore, the MPR can be used to identify CML patients who do not have their medications available for administration. Combining two methods can make the evaluation more robust.[27]

In respect of pharmacotherapeutic characteristics, we did not identify studies that evaluated the complexity of pharmacotherapy in patients with CML. However, similar data were found about the presence of comorbidities: 53.5% (n = 1407) in a study conducted in Hungary aimed at providing evidence on the characteristics, treatment patterns, and outcomes of patients with CML.[28] The presence of multiple chronic conditions can lead to the complexity of therapeutic regimens, which in turn can make pharmacotherapy management challenging and contribute to reduced treatment adherence. This, in turn, can lead to suboptimal pharmacotherapeutic outcomes and be an important factor in managing CML treatment. Evidence suggests that in patients with CML, the presence of comorbidities can impair treatment adherence[29] and consequently affect therapeutic outcomes and survival.[6]

To our knowledge, although some aspects of patient knowledge regarding TKIs have been investigated in previous studies,[14,15] our study was pioneering in analyzing various aspects of the relationship between knowledge and adherence in patients undergoing different treatment regimens. In our study, the fact that few patients had low knowledge about TKIs may be attributed to the pharmaceutical care service provided in the outpatient clinic, which focused on educating and supporting patients. However, other factors may have also influenced adherence, such as personal beliefs and the sociocultural context of the patients. A clinical trial conducted in Malaysia revealed that, among patients with CML, adherence was influenced by beliefs in medicinal plants and the difficulty of integrating the medication into daily life activities.[30]

Our study suggested that patients who do not know what to do in case of missing doses of TKIs tend to have lower adherence. We did not identify studies directly evaluating this relationship in patients with CML, but in this patient profile, forgetfulness was identified as the main cause of non-adherence, accounting for 38% of cases.[14] Furthermore, a study conducted in primary care identified that the "attitude in case of forgetfulness" was incorrect in 71.1% of cases.[31] Improving adherence is a team effort involving patients, family members, and healthcare professionals. Early identification of these predictors helps identify specific patients at risk of low adherence, who may, among other factors, need more information to deal with their disease and treatment.[32]

Concerning gender as a predictor of adherence, our findings differed from those of other studies. A study conducted with Taiwanese patients with CML did not identify a relationship between gender and adherence.[33] Another study investigating predictors of adherence in newly diagnosed patients found that women were more likely to be in the non-adherent patient group.[12] These differences may be partially explained by the fact that the adherence metrics used in the studies were divergent, Morisky's 8-item questionnaire, and proportion of days covered, respectively. These results reinforce the importance of choosing the appropriate adherence metric. Identifying predictors in different healthcare contexts and populations is important for developing targeted strategies to improve.[12]

Our study has several strengths. It was conducted in a specialized outpatient clinic, where probabilistic and stratified sampling allowed for the inclusion of a representative and unbiased sample. Data collection was conducted by a specialized team of pharmacists. However, some limitations were identified. For example, there was a lack of information in medical records, including BCR-ABL data. Additionally, the distance between patients' residences and the medication pickup location was not assessed due to possible patient omission of their residential location, likely due to fear of losing medication pickup benefits which are provided at no cost through the Unified Health System (SUS). Therefore, further studies are needed to investigate patient access-related factors that may influence adherence to TKI, as well as to assess which evaluation method is most suitable for this population.

Conclusion

We identified that adherence to TKI may differ depending on the method used for assessment. While the Morisky test revealed a non-adherence rate of approximately 56%, the MPR was around 25%. Significant predictors of low adherence included male gender, presence of comorbidities, and lack of knowledge about what to do if a dose is missed. Conversely, a longer time since diagnosis is associated with a lower likelihood of low adherence.

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Author contributions

Study conception and design: ACFM and TXAMF. Data collection: PRM, LTF, RGC, SPL, MMP. Data analysis: ACFM, LTF and PRM. Article writing: PRM, ACFM. Final article approval: PRM, ACFM, TXAMF, LTF, RGC, SPL, MMP.

Data availability statement

The data underlying this article will be shared on request to the corresponding author

Data access statement

The authors have full and continuous access to the study data. The database was created in Research Electronic Data Capture (REDCap).

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hospital of Clinics, Federal University of Goiás - UFG under protocol number 14964619.1.0000.5078. All participants agreed to take part in the study and signed the informed consent form.

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