



## Patient adherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia: influence of coping strategies and psychological factors

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### Original Article

#### Abstract

**BACKGROUND:** Medication non-adherence is associated with poor health outcomes and increased healthcare costs. Although the use of tyrosine kinase inhibitor (TKI) for chronic myeloid leukemia (CML) treatment is satisfactory in clinical results, it is subject to non-adherence. In this study, we intend to verify if there are psychological factors, such as anxiety, depression, and coping style that can influence medication adherence.

**METHODS:** The study was conducted on 120 patients with CML receiving long-term TKI therapy. The sample was collected in the years 2016-2017 at Department of Oncology-Hematology in Pescara, Italy. Adherence behaviour was measured with the eight-item Morisky Medication Adherence Scale (MMAS-8) and psychological factors investigated included: anxiety and depression symptoms [Hospital Anxiety and Depression Scale (HADS)] and coping strategies [abbreviated version of the Coping Orientation to Problems Experienced (Brief-COPE)]. T-test and logistic regression analyses were performed to investigate factors associated with medication adherence.

**RESULTS:** The participants, 74 men and 46 women, reported a mean age of  $56.65 \pm 15.80$  years. The results showed that 71.67% of the patients were adherent while 28.33% were non-adherent. Furthermore, adherence was positively associated with active coping ( $P < 0.050$ ) and instrumental support ( $P < 0.001$ ). Also, depression symptoms were risk factor for non-adherence ( $P < 0.050$ ).

**CONCLUSION:** This study suggests that active coping strategies with a good level of instrumental support are factors associated with greater adherence to long-term therapy. The results of this study support paying attention to factors identified as being helpful in monitoring patients with a risk of non-adherence. There is a need to provide increased psychosocial support for patients with chronic disease by planning effective client-focused interventions.

**KEYWORDS:** Adherence; Chronic Myeloid Leukemia; Coping Strategies; Anxiety; Depression

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#### Introduction

The use of the new tyrosine kinase inhibitor (TKI) has revolutionized the treatment of chronic myeloid leukemia (CML). Since the advent of

TKI, patients with CML had significantly improved prognosis. Although most patients treated with TKI have durable responses, resistance and side effects occur in some patients. This induces the patient to postpone or refuse the treatment. This is the reason why today there is a great difficulty in achieving an adequate therapeutic compliance.<sup>1</sup> According to the World Health Organization (WHO), approximately 50% of chronically ill patients who undergo long-term treatment are non-adherent to their

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medication and non-adherence is related with poor health outcomes and increased healthcare costs.<sup>2</sup> A systematic review about adherence in patients with hematological malignancies reports adherence rates between 20%-53% in patients with CML and non-adherence rates of 6%-35% in patients with acute lymphoid leukemia (ALL).<sup>3</sup> In addition, socio-economic factors are found to be associated to medication non-adherence.<sup>4,5</sup> A recent study shows how in patients with CML treated with imatinib (IM) for some years, poor adherence may be the predominant reason for inability to obtain adequate molecular responses. In addition, optimal drug adherence was associated with positive health outcomes.<sup>6</sup> Another study shows that the higher the adherence, the lower the level of breakpoint cluster region gene (BCR) at chromosome 22q11 to the Abelson gene (ABL1) (BCR-ABL1), but there are not many studies that investigate the influence of psychological factors on adherence.<sup>7</sup>

Coping strategies influence non-adherence and comorbidities in patients with chronic disease.<sup>8</sup> Exploration of these influencers has important implications for health education. Coping refers to the way an individual engages, both behaviourally and cognitively, to attenuate the impact of a stressor.<sup>9</sup> Coping is most commonly divided into two patterns: active (or problem-focused) and passive (or emotion-focused). Preceding studies have shown that people who respond with acceptance, positive reinterpretation, and problem-focused coping appear to be correlated to better psychological condition and better illness outcome, whereas a passive coping style is correlated with worse illness outcome.<sup>10</sup>

Other psychological factors associated with poor adherence are depressive and anxiety symptoms. A recent study shows the depressive trait as independent predictor of medication adherence.<sup>11</sup> Also, the results indicate that patients with psychological distress are at increased risk of non-adherence, and could therefore benefit from extra attention from the

healthcare professionals. Patients with symptoms of anxiety and/or depression should be identified and monitored in order to improve adherence to medication regimens. The assessment of anxiety and depression in patients with acute leukemia since hospital admission is substantial for the adherence to treatment.<sup>12</sup>

Therefore, this cross-sectional study looked at patients with CML hospitalized in the Department of Oncology-Hematology, UOC Clinical Hematology, Regional Authority of Abruzzo, Pescara, Italy. The hypothesis is that non-adherent patients manifested more depression and anxiety symptoms compared to adherent patients, and that some coping strategies can be predictors of a good adherence. Therefore, the aim of this study is to determine the relationship of coping styles, anxiety, and depression with adherence in patients with TKIs treatment.

## Materials and Methods

The study was submitted and approved by the Ethical Committee with the name of "Observational study of psychological factors: Adherence in treatment with TKI in CML". The research protocol was also authorized by the Ethics Committee (code: LMC-QoL01 of 28/09/2015) of ASL of the General Hospital in Pescara. The research was conducted with respect for the rights of all participants and the data were analysed entirely anonymously. Thus, all 120 participants were volunteers who filled out the questionnaires in a confidential setting.

A consecutive and unselected sample of 122 patients in the Department of Oncology-Hematology of the Civil Hospital, in Pescara was recruited in the years 2016-2017. Of the 122 recruited patients, 120 (98.3%) accepted to be enrolled. There are no missing data. Therefore, the sample consisted of 120 patients of both genders with a medically-documented diagnosis of CML, in the first line of treatment with TKIs, according to the diagnostic criteria of the WHO. Patients taking part in this study were

hospitalized in the UOC Clinical Hematology and all patients were contacted by clinical psychologists in collaboration with medical hematologists. We included patients of both sexes who met the following inclusion criteria: a) adult patients with an age ranging from 18 to 75 years, b) diagnosis of CML, and c) patients in treatment with TKI for at least six months. By contrast, patients with severe addictions and neurological or psychiatric disorders were excluded from the study. Moreover, patients suffering from CML previously submitted to bone marrow transplantation (BMT) and patients with CML who had undergone TKI for less than 6 months were excluded from the study. All participants completed the following self-rating scales: Hospital Anxiety and Depression Scale (HADS), abbreviated version of the Coping Orientation to Problems Experienced (Brief-COPE), and eight-item Morisky Medication Adherence Scale (MMAS-8).

The demographic and social factors such as age, gender, and housing situation were collected at baseline (i.e., at the time of diagnosis) (Patient Advocacy and Research Ethics). The clinical outcomes including the years of therapy, monitor, report, respond, and remedy ate (MR3), anxiety, and depression were obtained from the patients' medical records.

The presence of depressive and anxiety symptoms was assessed using clinical interview and self-report HADS.<sup>13</sup> HADS scale was used to measure anxiety and depression levels and consisted of two subscales. Both of them were structured of seven items scored from 0 to 3. Out of a possible 21 points, 0-7 points were considered normal, scores ranging between 8 to 10 were considered borderline, and > 11 points indicate severe symptoms of anxiety and depression.

The MMAS-8,<sup>14</sup> a standardised test, was used to measure adherence. Patients who scored 8 points, < 8 to > 6 points, and ≤ 6 points on the scale were considered to have high, medium, and low adherence,

respectively. This test has been developed from the well-validated Morisky-Green Test and The eight-item Morisky Medication Adherence Scale (MMAS-8). The internal consistency reliability of the Italian version of 8-item MMAS, measured by the Cronbach's  $\alpha$ , had a value of 0.89. The MMAS is composed of 8 questions that explore adherence behaviour based on forgetfulness, negligence, interruption of drug intake, and restart when symptoms worsen. This definition of adherence is based on how patients theoretically would have completed the MMAS if they had taken at least 95% of prescribed doses.

The Brief-COPE<sup>15</sup> is a self-report, validated, 28-item questionnaire that evaluates state coping, which is the manner in which an individual copes in response to a specific situation (i.e., the cancer diagnosis). It consist of 14 subscales (2 items per subscale) measuring the following: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioural disengagement, venting, positive reframing, planning, humour, acceptance, religion, and self-blame. Cronbach's  $\alpha$  ranges from 0.50 to 0.90 for the Brief-COPE subscales. Each single item is scored along a 4-point scale with the following options: 1) I usually do not do this at all, 2) I usually do this a little bit, 3) I usually do this a medium amount, and 4) I usually do this a lot. The following 8 subscales are classified as adaptive strategies: active coping, planning, positive re-framing, acceptance, humour, religion, use of emotional support, and use of instrumental support. The remaining 6 subscales are considered to be maladaptive and include self-distraction, denial, venting, substance use, behavioural disengagement, and self-blame. The maximum score for the 14 subscales is 8 points, with a higher score indicating greater use of a specific coping strategy.

A 3-step strategy was used for data analysis. First, socio-demographic and clinical variables

between adherent and non-adherent patients were compared using Student's t-test or chi-square test, and effect sizes were expressed as standardized mean differences. A standardized effect size (Cohen's *d*) of 0.20-0.50 is considered small, 0.50-0.80 moderate, and  $> 0.80$  is considered large. The reliability of the applied scales was assessed using Cronbach's  $\alpha$  coefficient. Second, binary logistic regression analysis was performed to identify major determinants that best predict the adherence; the letter as a dependent variable (dummy coded: 0 = low adherence, 1 = adherence) and the independent variables were age, sex, years of therapy, depression, and anxiety symptoms and coping strategies. Four regression models were processed and regression coefficients, the related confidence intervals (CIs), odds ratios (ORs), and P-values were estimated. We also calculated the  $R^2$  coefficient value for each of the adjusted models. Third, direct maximum likelihood (ML) confirmatory factor analysis (CFA) was used to examine the construct validity of the Italian MMAS-8 scale. Data were analysed using Stata software (version 13, Stata Corporation, College Station, TX, USA) at the statistical significance level of  $P < 0.050$ .

## Results

120 participants reported a mean age of  $56.65 \pm 15.80$  years, with ages between 23 and 75 years and were predominantly men ( $n = 74$ ). Most of the participants resulted to be currently married ( $n = 104$ ) and the participants of the study were assessed for years of therapy that showed an average of 6.30 [standard deviation (SD) = 4.6] years. Table 1 reports the comparisons between adherent and non-adherent patients. According to our results, 71.67% of patients were considered as adherers; therefore, they regularly followed the recommended drug therapy, while 28.33% of the patients presented non-adherence to the drug therapy. To check the reliability of the factors (psychological dimensions), Cronbach's  $\alpha$  coefficients were

computed. The results showed that Cronbach's  $\alpha$  resulted greater than 0.70 for all the factors, meaning that each factor scale had consistency. No between-group significant differences were found in socio-demographic and clinical (years of therapy) characteristics. The two subgroups of patients, adherent and non-adherent, were markedly different when they were evaluated for active coping, emotional and instrumental support, with low effect sizes in the small range. Adherent patients reported significantly higher active coping and emotional and instrumental support scores than non-adherent patients ( $5.64 \pm 1.73$  vs.  $5.27 \pm 1.94$ ,  $4.40 \pm 1.88$  vs.  $3.97 \pm 1.74$ ,  $4.97 \pm 1.97$  vs.  $4.27 \pm 1.97$ , respectively) with effect size of  $d = 20$ ,  $d = 23$ , and  $d = 35$ , respectively. Same significant between-group differences were found for the depression symptoms but not the anxiety trait. Moreover, non-adherent patients had significantly higher depressive ( $9.63 \pm 6.03$ ) scores than the adherent group ( $5.31 \pm 4.56$ ) ( $d = 0.32$ ). A significant difference was found between groups for MR3 clinical variable ( $P < 0.001$ ) (Table 1).

4 regression models with adherence score as binary outcome were explained. The first model with age and sex, as principal predictors, explained a small part of the adherence variance ( $R^2 = 0.04$ ). The second model was adjusted with years of therapy and MR3 variables adding 17% to the explained variance (OR = 1.03). The third model adjusted for depressive and anxiety scale explained a major part of the variance ( $R^2 = 0.19$ ). The final model, adjusted for emotional support, active coping, and instrumental support scores predicted 22% of the explained variance (OR = 0.95, OR = 1.02, OR = 1.32, respectively). The results showed that depression symptoms ( $P \leq 0.050$ ) were risk factors of non-adherence, but active coping ( $P \leq 0.050$ ) and instrumental support ( $P \leq 0.001$ ) were significant predictors of adherence. No significant results were found for age, gender, years of therapy, anxiety symptoms, and emotional support variables (Table 2).

**Table 1. Socio-demographic and clinical characteristics of the study sample: Comparison with adherence (n = 120)**

Variable		Total sample (n = 120)	Adherence (n = 86)	Non-Adherence (n = 34)	t/ $\chi^2$	P	Cohen's d
Gender	Men	74	52 (60.47)	22 (64.71)	-0.42	0.670	0.08
	Women	46	34 (39.53)	12 (35.29)			
Housing situation	Living alone	16	12 (13.95)	4 (11.77)	0.31	0.750	0.18
	Living with others	104	74 (86.05)	30 (88.23)			
MR3	Yes	107	84 (97.67)	23 (67.64)	5.25	< 0.001	0.80
	No	13	2 (2.33)	11 (32.36)			
Age (year)		56.65 ± 15.80	57.49 ± 15.42	54.61 ± 16.98	-0.88	0.370	0.18
Brief-COPE	Active coping	5.38 ± 1.88	5.64 ± 1.73	5.27 ± 1.94	1.96	< 0.001	0.20
	Planning	5.45 ± 2.10	5.47 ± 2.17	5.38 ± 1.93	-0.22	0.820	0.04
	Positive refraining	5.63 ± 1.99	5.60 ± 2.11	5.70 ± 1.67	0.24	0.800	0.05
	Acceptance	7.15 ± 1.40	7.17 ± 1.48	7.08 ± 1.21	-0.30	0.760	0.06
	Humour	3.92 ± 1.76	7.89 ± 1.77	4.00 ± 1.75	0.29	0.750	0.05
	Religion	5.15 ± 2.26	5.24 ± 2.26	4.94 ± 2.29	-0.66	0.500	0.13
	Emotional support	4.28 ± 1.85	4.40 ± 1.88	3.97 ± 1.74	1.16	< 0.001	0.23
	Instrument support	4.78 ± 1.99	4.97 ± 1.97	4.27 ± 1.97	-1.74	< 0.001	0.35
	Self-distraction	5.00 ± 1.98	5.10 ± 2.02	4.76 ± 1.89	-0.84	0.400	0.17
	Denial	2.90 ± 1.66	2.93 ± 1.74	2.85 ± 1.45	0.22	0.810	0.04
	Venting	4.11 ± 1.86	4.77 ± 1.89	3.73 ± 1.78	-1.42	0.100	0.28
	Substance use	2.12 ± 0.64	2.16 ± 0.74	2.03 ± 0.17	-1.01	0.310	0.20
	Behavioural disengagement	3.11 ± 1.68	3.19 ± 1.67	2.91 ± 1.71	-0.83	0.400	0.16
	Self-blame	3.88 ± 1.49	3.86 ± 1.59	3.96 ± 1.21	0.32	0.740	0.07
Years of therapy		6.30 ± 4.64	6.46 ± 4.67	5.86 ± 2.01	0.59	0.550	0.12
HADS-D		6.56 ± 5.26	5.31 ± 4.56	9.63 ± 6.03	-5.21	< 0.001	0.32
HADS-A		6.61 ± 3.80	6.45 ± 3.84	7.02 ± 3.74	0.74	0.450	0.15

Data are presented as mean ± standard deviation (SD) or number and percentage

MR3: monitor, report, respond, and remediate; COPE: Coping Orientation to Problems Experienced; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale

At last, the CFA showed satisfactory construct and results pointed to a one-factor solution in all the items contributed to the final

index of adherence. Accordingly, the Italian version of the MMAS-8 is a reliable and valid measure of medication adherence (Table 3).

**Table 2. Predictors of adherence, results of binary regression models (n = 120)**

Variables	$\beta$	OR (95% CI)	P	R <sup>2</sup>
Model 1				0.04
Age	0.01	1.01 (0.98-1.03)	0.950	
Gender	0.28	0.64 (0.28-1.46)	0.290	
Model 2				0.17
+ Years of therapy	0.03	1.03 (0.93-1.13)	0.640	
+ MR3	0.73	1.11 (0.95-1.19)	< 0.001	
Model 3				0.19
+ HADS-A	0.05	0.95 (0.83-1.11)	0.440	
+ HADS-D	-0.11	1.02 (0.85-1.13)	< 0.050	
Model 4				0.22
+ Emotional support	0.04	0.95 (0.78-1.35)	0.790	
+ Active coping	0.15	1.02 (1.05-1.09)	< 0.050	
+ Instrumental support	0.30	1.32 (0.94-1.85)	< 0.001	

HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; OR: Odds ratio; CI: Confidence interval

**Table 3. Factor loading patterns of the Italian eight-item Morisky Medication Adherence Scale (MMAS-8) (n = 120)**

Item as numbered in the original MMAS-8	Items loading
1. Do you sometimes forget to take your medications?	0.61
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?	0.73
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?	0.44
4. When you travel or leave home, do you sometimes forget to bring along your medication?	0.59
5. Did you take your medicine yesterday?	0.32
6. When you feel like you are under control, do you sometimes stop taking your medicine?	0.62
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	0.40
8. How often do you have difficulty remembering to take all your medications?	0.28

Values in bold are those with a loading at 0.32 or higher on a factor which means that they pertain to this factor  
MMAS-8: Eight-item Morisky Medication Adherence Scale

### Discussion

Patients with chronic disease could have different elapses and evolutions, not always explainable with organic factors or with objective differences of environmental or social contexts. The way in which the patient can give a meaning to the drug, which is both slavation (Patient Advocacy and Research Ethics) and limit, will have great importance for the whole run of his/her own illness. In psychology, adherence is a process by which individuals create their own balance or at least, an absence of conflict, with the environmental conditions. The adherence of patients with chronic illness is a mediator among the psychological, social, environmental, and physical characteristics that plays a crucial role. A complete adherence is the moment when the patient is included in his/her life medicine and the disease.<sup>16</sup>

Given the paucity of data in the CML literature, we selected possible factors associated with adherence behaviour based on previous studies in other chronic medical conditions. Evidence from other studies on adherence in chronic patient populations showed that younger age was associated with lower adherence as well.<sup>17</sup>

There are a number of studies which focused on anxiety and depression in cancer; however, the same interest is not observed in

the field of hematologic malignancies. This study was to test the prevalence of adherence to TKI treatment in patients with CML and evaluate psychological factors (anxiety and depression traits) associated with adherence. The second step was to explore the association between coping styles as predictors of adherence. The results confirm that patients with a good level of adherence are 71.67% of the observed group. Furthermore, the results confirm that in CML therapy, a good adherence is essential for a successful treatment. However, this element decreases with the increase of the years of treatment for both sexes, but in our study, it is not statistically significant.

Psychological and medical supports at the time of diagnosis and during treatment are essential to revitalize the patient's desire to live and increase the adherence to treatment.<sup>12</sup> The study of psychological dimensions in patients with CML showed that some coping strategies were potentially significant for the definition of adherence. A recent study by Conti *et al.* shows that increasing the depression levels decreases the medication adherence;<sup>18</sup> and also from our results, it is observed that depression is a risk factor for low adherence.

As for the coping behaviour, it has been shown that the use of the active coping strategies (positive reappraisal, self-

controlling) helps patients with cancer to significantly reduce the level of anxiety and depression caused by the uncontrollable threat to life and the high uncertainty of the disease situation. It has been indicated that excessive use of an avoidance coping style can easily produce negative emotions and then affect treatment adherence.<sup>19</sup> The use of passive emotional-oriented coping strategies such as avoidance is often associated with low adherence to treatment in patients with chronic disease. In a recent study, even a negative effect of the avoiding coping on outcome of cancer was found.<sup>20</sup> As well, in this study, we found a positive relationship between adherence and patient's coping strategies; patients showing greater adherence frequently use coping strategy as: active coping and instrumental support. Binary regression analysis reflected the need for developing strategies to strengthen instrumental support and active coping as a factor in promoting adherence to treatment, but it shows that patients with high levels of depression have low adherence to therapy. Therefore, depression symptoms can be risk factors for health outcomes.

This study contributes to the growing literature on the effect of depression symptoms and coping style on adherence. Our results imply that interventions that improve coping style and better adherence may lead to improved health outcomes and should thus be explored. Hence, to prevent negative emotions and treatment non-adherence in the future, psychological interventions should be conducted to improve the coping style of haematological patients. We can say that psychological support improves adherence.

Another limitation of the study was that due to its cross-sectional nature, it only explains the relationship between the variables affecting adherence and is not capable of showing the sequence. Longitudinal studies could provide more insight into the underlying mechanism of the relationships

found in this study.

### Conclusion

Patients with symptoms of anxiety and/or depression should be identified and monitored in order to improve adherence to medication regimens. In conclusion, the regression models explained less than 22% of the variance of the study outcome. Therefore, further research is required to explore which additional factors can determine coping styles and adherence among patients with CML.

**Limitations:** This study is not without limitations. First, because it was conducted in a relatively small group of inpatients treated in a single health facility, its results are applicable only to the patients surveyed, and thus, they cannot be generalized to other patients. Second, we relied exclusively upon self-report measures for assessing our constructs and the use of self-reporting for data selection, so the participants' answers might be subject to social desirability bias.

### Conflict of Interests

Authors have no conflict of interests.

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