

Adherence and future discontinuation of tyrosine kinase inhibitors in chronic phase chronic myeloid leukemia. A patient-based survey on 1133 patients



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ABSTRACT

Therapeutic approach for chronic myeloid leukemia (CML) patients has undergone a revolutionary change with the introduction of tyrosine kinase inhibitors, which improved overall survival and quality of life. Optimal therapy adherence has become of paramount importance to maximize the benefits in the long-term outcome. Several evidences have been reported that personal factors, such as social support, psychological and subjective perceptions about the drug used and the future, could influence adherence. We here report the results of a questionnaire specifically designed to evaluate factors influencing adherence and perceptions about the future, distributed to patients during regional Italian meetings. Overall, 1133 patients compiled the questionnaire: median age was 57 years. High rate of adherence was reported, but 42% of interviewed patients admitted that they had occasionally postponed a dose and 58% had discontinued therapy mainly for forgetfulness. The majority of patients discussed with personal physician about the importance of adherence and received sufficient information about illness and treatment, but would like to have discussed more about discomfort, anxiety and fear of the future. Summarizing personal drug compliance and estimating how many days a month, on average, the patients did not take the drug, the majority answered that it was less than 3 days (55%) and only a minority (4%) admitted that it was more than 7 days. Interviewed about discontinuation, 49% of patients answered that wouldn't interrupt because of fear of losing all the results achieved so far. This study suggests a higher level of satisfaction with more information received but the need of improving communication about possible future treatment free remission.

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1. Introduction

Imatinib was the first molecular targeted therapy (i.e., tyrosine kinase inhibitors (TKIs) approved by the US Food and Drug administration (FDA) for chronic myeloid leukemia (CML) in early 2000. This drug dramatically improved CML patient outcomes by showing major clinical advantages and improved quality of life (QoL) compared to previous treatments, such as interferon (IFN) [1,2]. However, as imatinib or other TKIs are to be administered on a daily basis, maintenance of optimal QoL over the long-term period, has become a critical aspect of care in this cancer population. Some studies have shown that QoL of CML patients treated with imatinib is similar with that of their peers in the general population for patients aged 60 years or older, but major limitations exist for younger CML patients in several aspects of daily life activities [3].

Another key challenge introduced by the introduction of TKIs in the treatment of CML patients is that of adherence to therapy. Indeed, low adherence was shown to be associated to decreased rate of cytogenetic and molecular responses and, consequently, increased rate of progression and resistance [4,5]. Some studies have shown that a large proportion of CML patients do not fully adhere with treatment [4] and that this could be explained by both intentional and unintentional reasons [6]. However, patient adherence has been collected in different ways amongst the few studies conducted so far, thus hampering a clear understanding of factors associated with medication-taking behavior. This is also further complicated by the fact that, measuring adherence to therapy is challenging and all methods have “pro” and “cons” [7–9]. Also, the interplay between all the potential factors that can contribute to improve adherence in CML is poorly understood and more data are needed on this topic.

Therefore, as in the CML arena very few studies addressed this issue in the real-world setting [10,11] we have performed a large patient-based survey to investigate adherence behaviors and potential relationships with QoL, treatment satisfaction, and social life. Also, we focused on patient's attitude toward the possibility of drug discontinuation in future treatment free programs.

2. Patients and methods

In a series of meetings developed only for patients, an ad hoc survey including 25 items was designed and proposed. Patients were recruited from physicians from different centers on a specific

invitation and therefore, based on the fact that were not selected, were representative of general CML population. The survey was designed based on real-life level of evidences and on literature review about adherence in CML. We included in the final analysis only questionnaires completely answered in each item. The items of the survey were grouped into the following board categories: (1) general questions about personal behavior; (2) relationship with treating physician; (3) perceptions of quality of life and adherence behaviors; (4) perceptions about future possible discontinuation of drug assumption. CML patients in treatment with any kind of TKI stemming from 30 Italian hematology centers: as some questions differed across centers, only the questions that were used in the majority of centers were analyzed. Overall, the analyzed questions from 28 centers were reported in this study: 13 centers from northern Italy, 7 from central Italy, 8 from southern Italy. Items included in the Survey are summarized in [Appendix A](#).

In the final analysis were also considered the following features requested at the time of survey completion: gender, age, level of education and disease's duration. Descriptive statistics were provided for questions considering all the questions reported in at least 6 centers. Categorical variables (gender, education and all the questionnaire questions) were summarized by using frequency distributions (i.e. the number of patients in each level of the categorical variable) and percentages. Quantitative variables (age and disease duration) were summarized by using n, arithmetic mean, standard deviation, median, range, minimum and maximum.

3. Results**3.1. Population characteristics**

Overall, 1133 patients completed the questionnaire, of them 658 males (58.1%) and 475 females (41.9%). Fifty-three percent of patients had a high level of education (high school-university), whereas 21% had only primary/elementary level and 25.7% a middle school level. Median age of patients was 57 years (range 17–90) and according to cumulative frequencies the most represented age category was that from 65 to 75 years (22.89%) followed by 55–65 years (21.72%) and 45–55 (19.75%). The majority of patients (79.55%) had a median duration of disease of less than 10 years.

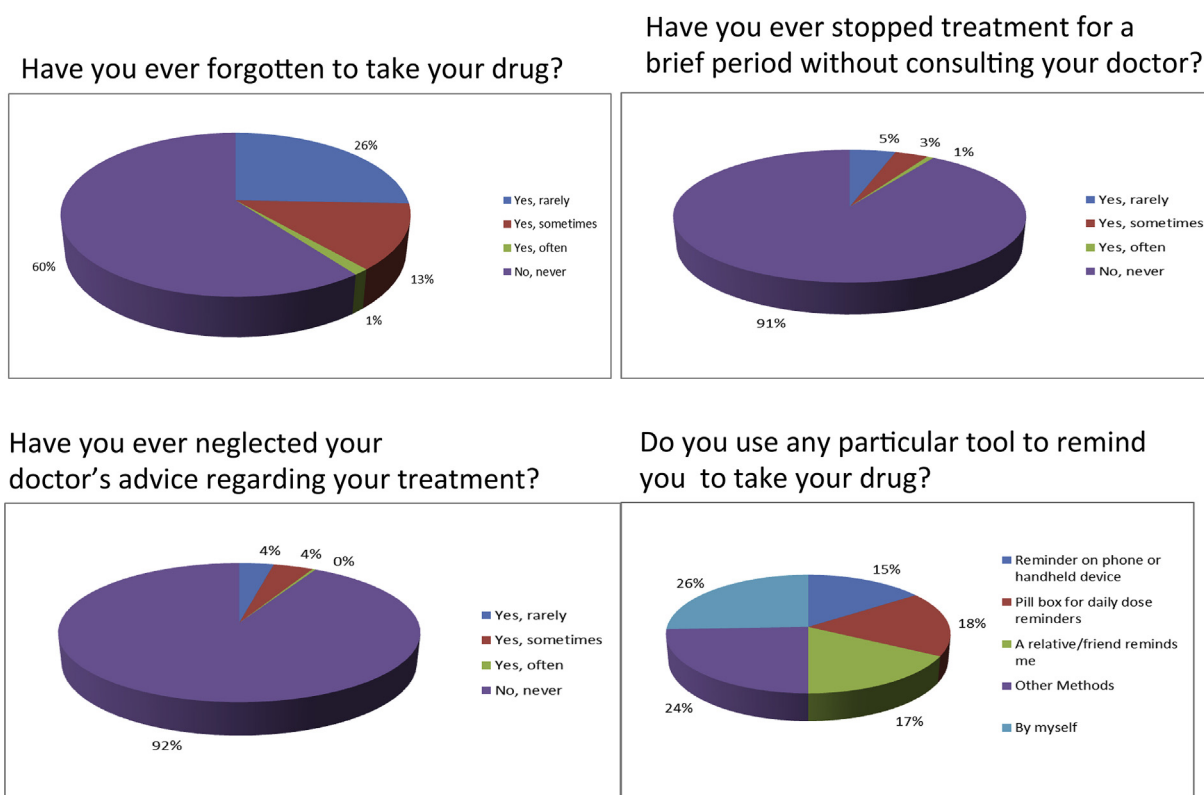


Fig. 1. Most relevant questions about adherence.

3.2. General questions about personal behavior

At first question (“Have you forgotten to take your drug?”), 60% of patients answer “no, never”, whereas 25.6% admitted that rarely forgot to take prescribed therapy. Ninety-one percent (91%) patients have never stopped treatment without consulting their treating physician.

Frequently, patients had occasionally postponed a dose (42.6%) and more rarely this was a continuative behavior (3.7%). Rarely, patients took other medicines or herbal products together with the drug (13% as occasional episode and 3% of patients answered “yes often”). Less than 1% of patients deliberately changed the drug dosage without agreeing with his/her doctor, whereas only 5% of patients forgot to refill in time the drug prescription. Only 4% of patients admitted that they had interrupted treatment due to a sense of wellness and, on the contrary, 8% of patients discontinued temporarily treatment due to an increase sense of illness after intake. The main reasons for discontinuation were forgetfulness (58%), side effects (14%), a sense to feel sick (5%), concomitance with other drugs (5.6%), but none answered that discontinuation was due to the fact that nobody had explained the importance to be adherent to therapy. Eighty-nine percent of patients were aware of the consequences of a scarce adherence (Fig. 1).

3.3. Relationship with treating physician and perceptions of quality of life and adherence behaviors

On the question “What issues related to the illness and treatment would you like to talk about but you can't”, the majority of patients (41%) reported that would like to discuss about discomfort, anxiety and fear of the future, 18.8% of patients about psychological problems, 12% about problems at work, 10% about relationship and family life and 9% of patients about sexual problems.

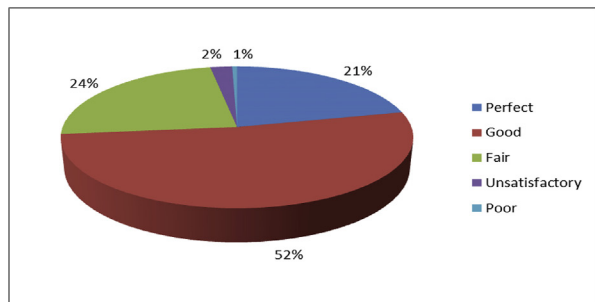
Several methods were used to remember to be adherent to the prescribed dose: 15% of patients used reminder on the phone or handheld device, 18% a pill box and 17% were helped by a relative or a friend; 26% of patients did not have the need to remind to take medication. Twenty-eight percent of patients admitted to be dependent from someone to be adherent to drug every day.

Only 21.5% of patients evaluated the state of QoL as perfect, 52% as good, whereas 24% classified own QoL as fair. A question investigated about family perceptions of illness: 44% of patients answered that own family was relaxed and confident, 52% that family was a bit worried, but confident and only 4% that own family was very worried about CML. Summarizing personal drug compliance and estimating how many days a month, on average, the patient did not take the drug, the majority answered that this was for less than 3 days (55%) and only a minority (4%) for either more than 7 days or between 4 and 7 days. As regards the importance of communication, the majority of patients (73%) believe that it would be important to share personal experience with other patients affected by CML and also believe that there's need to organize regular meetings regarding CML (Fig. 2).

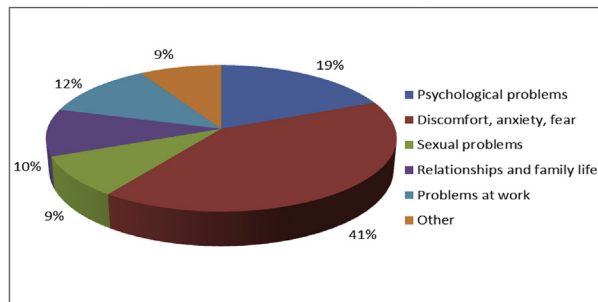
3.4. Perceptions about future possible discontinuation of drug assumption

At the question “If in the future there is a perfect and long-lasting response to the treatment, would you accept the opportunity to interrupt the treatment for your illness?”, 49% of patients answered that wouldn't interrupt it because afraid of losing all the results achieved so far, whereas 16% of patients would like to discontinue due to long-term intolerance and 20% didn't make difference between possible discontinuation and to continue with the daily drug.

How would you evaluate your quality of life in relation to the treatment and the illness?



What issues related to the illness and treatment would you like to talk about but you can't?



If in the future there is a perfect and long-lasting response to the treatment, would you accept the opportunity to interrupt the treatment for your illness?

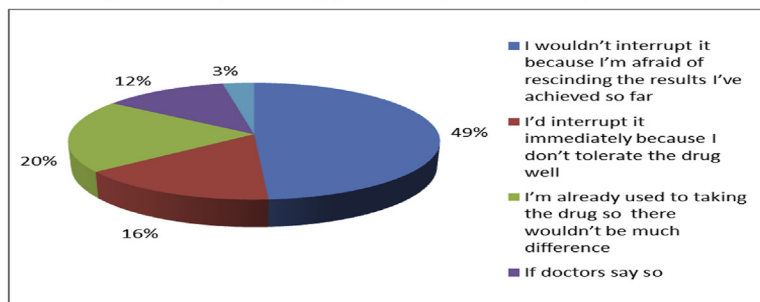


Fig. 2. Most relevant questions about QoL.

4. Discussion

The results of this large patient-based survey indicate that participants who receive routinely imatinib or other TKIs accepted CML as a chronic disease and were generally adherent to treatment. Forgetfulness and side effects were the main reasons for which patients altered imatinib therapy. Participants also admitted to be aware of non-adherence consequences and also indicated good communication during routine outpatient visits.

Importantly from this survey emerged that patients often wish to discuss with their physicians about discomfort, anxiety and fear of the future, and also other psychological problems. This is an important finding as often these issues are not part of routine visits and additional psychological counseling might be necessary to further help CML patients to cope with the disease and the fear of disease progression.

Eliasson et al. reported intentional and unintentional reasons for non-adherence and showed that factors that seemed to favor adherence were dealing with side effects and using prompts as reminders to take medicine [6]. Our results reinforced those observed as results of the interviews conducted by the Hammer-smith group as well as by other groups [6,10,12]. Side effects associated to poor adherence can be managed by prompt attention and supportive care. Our study could be limited by some bias: a self-reported questionnaire may have influenced the results of the survey reported here (the so-called "Hawthorne effect") [13]. Most studies rely upon self-reporting by patients suffer from the bias to overestimate the rates of adherence (unwillingness to admit a scarce adherence), and were considered by some authors too subjective [14,15,7]. Another possible bias to keep in mind is the rate of participation to the scheduled events: we estimated that the rate of adherence to this survey was higher than 85%, therefore this bias could not invalidate the messages of this study.

Another area we aimed to explore in this survey was patients' attitude toward the possibility of stopping drug assumption. Indeed, with the introduction of second generation TKIs and the achievement of deeper molecular responses, it is possible to hypothesize a future discontinuation. Several studies showed that from 40 to 50% of patients who discontinued imatinib, remained in molecular response without relapse if discontinuation occurred in deep long-lasting molecular response [16–20]. Very recent CML protocols are also further testing this possibility [21]. The results of this study showed that patients are aware of the possibility to discontinue TKI treatment but the majority of them (49%) would be reluctant to interrupt therapy because afraid of losing response to therapy. We can speculate on these results that healthcare physicians should improve patient's knowledge on making appropriate judgment as to long-term effects from treatment, dealing with missing doses and adverse effects reinforcing the importance of adherence. Moreover, increased knowledge about treatment free remission is necessary in order to illustrate the importance of deep molecular response and possible discontinuation.

Authors' contributions

MB analyzed data and wrote the paper; all the other authors followed patients that performed questionnaires; FE and GA critically revised the paper.

Conflict of interest statement

All authors have no conflict of interest to report.

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Appendix A.

A.1. Items included in the ad-hoc Survey

- (1) Have you ever forgotten to take your drug?
- (2) Have you ever stopped treatment for a brief period without consulting your doctor?
- (3) Have you ever postponed a dose of medication after the scheduled time?
- (4) Have you ever taken other medicines, nutraceuticals, vitamins or herbal products, together with the drug without your doctor's knowledge or without consulting him/her first?
- (5) When and how often are you able to discuss your illness with your doctors?
- (6) Have you ever deliberately changed the drug dosage without agreeing with your doctor?
- (7) Do you have the possibility to speak openly with your doctors about your treatment?
- (8) Have you ever forgotten to refill your drug prescription in time?
- (9) Have you ever depended on someone to remind you to take your drug?
- (10) Would it be important for you to share your experience with other people affected by CML?
- (11) Have you ever neglected your doctor's advice regarding your treatment?
- (12) Would you like regular meetings regarding CML to be organized between doctors and patients?
- (13) Have you ever interrupted your treatment because you were feeling better?
- (14) Do you use any particular tool to remind you to take your drug?
- (15) Have you ever decided to suspend your treatment because you were not feeling well after intake?
- (16) If you replied Yes to any of the above questions, what was the reason?
- (17) Are you aware of the consequences you risk if you don't take your drug correctly?
- (18) Do you believe you've received sufficient information from your medical team?
- (19) Who supplies you with the drug in the center where you're being treated?
- (20) In order to summarize your drug compliance, how many days a month, on average, did you not take your drug correctly?
- (21) How would you evaluate your quality of life in relation to the treatment and the illness?
- (22) What issues related to the illness and treatment would you like to talk about but you can't?
- (23) How does your family feel about your illness?
- (24) Do you find that you have to limit yourself in certain daily activities due to your illness?
- (25) If in the future there is a perfect and long-lasting response to the treatment, would you accept the opportunity to interrupt the treatment for your illness?

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