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Profiling chronic myeloid leukemia patients reporting intentional and unintentional non-adherence to lifelong therapy with tyrosine kinase inhibitors

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ABSTRACT

The main objective of this study was to outline key characteristics, including health-related quality of life (HRQOL) and symptoms, in 175 chronic myeloid leukemia (CML) patients reporting intentional or unintentional reasons for not fully adhering to imatinib therapy. There was a significant higher proportion of males in the unintentional group ($P = 0.037$). Also, in this group patients were on average younger ($P = 0.046$). Patients reporting intentional reasons had generally a worse HRQOL profile and a higher symptom severity than those who reported unintentional reasons for non-adherence. This study suggests that patients with suboptimal adherence are not a homogenous group, thus generalized approaches to improve medication-taking behaviors are not recommended.

1. Introduction

The development of molecular targeted therapies (i.e., oral tyrosine kinase inhibitors [TKIs]) to treat chronic myeloid leukemia (CML) is one of the great triumphs of modern oncology. However, long-term continuous exposure to the TKIs is necessary and optimal adherence to therapy is crucial to boost clinical outcomes [1,2]. To illustrate, Marin and colleagues [2] found a correlation between low adherence rate (≤90%) and 6-year probability to achieve a major molecular response (MMR) and a complete molecular response (CMR). Adherence can be defined as "the degree or extent of conformity to the recommendations about day to day treatment by the provider with respect to the timing, dosage and frequency" [3].

The proportion of CML patients who do not adhere to treatment schedule is substantial ranging from 30% to 47% [1,4]. However, very little research has been conducted to identify factors associated with medication-taking behavior in CML [4,5].

To better address the problem, researchers have distinguished between two types on non-adherence, that is, intentional and unintentional non-adherence [6]. Specifically in the CML setting, Eliasson and colleagues have recently indicated that also CML patients report both intentional and unintentional reasons for not adhering to treatment [7]. Intentional reason was defined as the patient deciding not to take the medication as prescribed while unintentional non-adherence was considered when the patient might have wanted to take the medication as prescribed by the physician but was unable to [7]. In their qualitative study they identified as major broad themes: *forgetfulness*, and *dealing with side effects* as the main reasons for unintentional and intentional non-adherence respectively [7]. The identification of subpopulations of CML patients, by type of non-adherence, has important clinical implications. For example, this would guide the development of targeted interventions to promote greater adherence and ultimately increase clinical effectiveness of TKIs.

Previous data has also showed that health-related quality of life (HRQOL) of CML patients receiving TKIs is impaired in many respects with several burdensome symptoms compromising daily life even several years since treatment start [8–11]. On this ground, we hypothesized an association between worse HRQOL and greater symptom severity in those patients reporting intentional reasons.

The main objective of this study was to outline HRQOL, symptoms, sociodemographic and clinical characteristics in patients reporting intentional or unintentional reasons for not fully adhering to imatinib therapy. Secondary objectives were to investigate

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prevalence of unintentional versus intentional non-adherence and to explore factors associated with intentional non-adherence.

2. Patients and methods

2.1. Study population and logistics

Patients were recruited in a large survivorship hospital-based multicenter study whose logistic details and recruitment procedures have been reported previously [8]. Inclusion criteria included a confirmed diagnosis of CML and duration of imatinib therapy for at least three years. Also, patients had to be in complete cytogenetic response (CCyR) at the time of study entry and not having psychiatric conditions or major cognitive dysfunctions hampering a self-reported evaluation. Ethic Committees of participating centers approved the study and all patients provided written informed consent.

2.2. Suboptimal adherence and intentional versus unintentional reasons

In our previous study, patients were categorized in two broad groups based on their medication taking behavior, that is, *optimal* versus *suboptimal adherers* and details are reported elsewhere [4]. Briefly, based on an adapted version of the Morisky Medication Adherence Scale (MMAS) [12], patients who reported that rarely, sometimes or often do not perfectly adhere to treatment, for whatever reasons, were classified as *suboptimal adherers*. In current analysis, these patients were further classified based on their stated reasons for not adhering exactly as prescribed by their physicians.

Patients were asked, in a non-judgmental fashion, the following questions as part of their survey on adherence behavior: "What is the main reason for which sometimes you might skip a dose?" Possible, mutually exclusive answers were: (1) forgetfulness; (2) dealing with side effects. Based on previous data [6,7], and for the purpose of this article, our population of *suboptimal adherers* was thus further classified as reporting respectively unintentional and intentional reasons for non-adherence.

2.3. Variables examined for their association with type of non-adherence

The following socio-demographic and clinical variables were examined for their association with type of non-adherence: age, gender, education, living arrangements, ECOG performance status, Sokal risk, comorbidity at the time of diagnosis and time from CCyR to adherence evaluation.

HRQOL was evaluated with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). This questionnaire consists of 36 items yielding eight scales: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH). The eight scales provide a score ranging between 0 and 100 with higher scores representing better health outcomes [13].

Symptom burden was evaluated with a previously reported ad hoc CML symptom survey [8,14]. The following symptoms were examined: abdominal discomfort, diarrhea, edema, headache, muscle cramps, musculoskeletal pain, nausea, skin problems and fatigue. Patients indicated on a four point Likert scale the extent to which they had been bothered: not at all, a little (i.e., mild), quite a bit (i.e., moderate) and very much (i.e., severe).

2.4. Statistical analysis

Current analysis is based on patients previously identified as *suboptimal adherers* ($N = 194$) [4]. Possible differences between intentional and unintentional non-adherers in socio-demographic and clinical characteristics were investigated by Fisher's exact or Wilcoxon–Mann–Whitney test as appropriate ($\alpha = 0.05$). Given the exploratory nature of this analysis, differences in symptom burden and HRQOL were not tested for statistical significance. Eight points were considered to be a minimally important difference (MID) for the SF-36 scales [15]. A score difference at least equal to MID was considered as a clinically meaningful difference. Univariate logistic regression analysis was performed to explore the possible impact of selected key patient characteristics, based on clinical relevance, on the probability of intentional non-adherence. After having checked for possible multicollinearity by the variance inflation factor, the same variables were included in a multivariate logistic model ($\alpha = 0.05$). All analyses were performed with SAS v. 9.1.3 (SAS Institute Inc., Cary, Inc.).

3. Results

Out of 194 patients considered suboptimal adherers in this study, 175 (90%) responded to the questions about reasons for non-adherence. Median age of the entire cohort of 175 patients was 54 years (range 20–87 years).

Forty-seven patients (27%) reported intentional reasons for not fully adhering to treatment (i.e., due to side effects) while 128 (73%) reported unintentional reasons (i.e., reasons other than avoiding side effects). There were no statistically significant differences in the two groups with regard to time from CCyR to adherence evaluation, ECOG performance status, Sokal risk and comorbidity at diagnosis, living arrangements and education. However, there was a significant higher proportion of males in the unintentional group ($P = 0.037$). Also, in this group patients were on average younger ($P = 0.046$). Details of patient population, by type of non-adherence, are reported in Table 1.

3.1. HRQOL and symptom burden by reasons for non-adherence

All mean scores of the eight scales of the SF-36 were lower (i.e., worse outcomes) in patients who reported intentional non-adherence. Although, given the explorative nature of this study, we did not apply any statistical testing, the magnitude of mean score differences was clinically meaningful (i.e., more than 8 points) in five out of the eight scales. These included physical functioning ($\Delta = 10.4$), general health ($\Delta = 10.3$), role physical ($\Delta = 8.1$), social functioning ($\Delta = 10$) and mental health ($\Delta = 9.2$). Details are reported in Table 2.

Investigation of pattern of symptoms revealed a tendency for a greater burden for patients who reported intentional reasons of non-adherence. To illustrate, moderate to severe muscular cramps were present in 43% of patients reporting intentional reasons for non-adherence while only 28% of patients reporting unintentional reasons rated the intensity of their muscular cramps as moderate to severe. Symptom severity by type of non-adherence to therapy is depicted in Fig. 1.

3.2. Factors associated with intentional non-adherence

The following variables were investigated for their association with intentional non-adherence: age, gender, living arrangements, education and time from CCyR. As severity of nausea and muscular cramps were found to substantially differ between groups in descriptive analysis (Fig. 1), these were also included.

In univariate logistic regression analysis, the following variables were statically significant associated with intentional non-adherence: gender ($P = 0.033$), nausea ($P < 0.001$), and muscular cramps ($P = 0.013$). In multivariate analysis, an older age ($P = 0.041$) and a higher severity of nausea ($P = 0.003$) independently predicted a greater likelihood of intentional non-adherence (Table 3).

4. Discussion

In this study we analyzed a CML population with suboptimal adherence and found that the majority of these (73%) reported unintentional reasons for not fully adhering to therapy. This data is broadly in line with similar research conducted in patients with other chronic diseases [6].

Current findings suggest that patients who do not fully adhere to imatinib are not a homogenous population. These patients broadly report intentional and unintentional reasons, which tend to be associated with different sociodemographic, HRQOL and symptom characteristics. This might suggest that generalized approaches to enhance adherence are not recommended. To illustrate, it is possible to speculate that physicians can have a major role in increasing adherence level in those patients who report intentional non-adherence, for example, by improving symptom management. Conversely, a better symptom management might not be highly effective to enhance adherence in those patients who typically tend to forget to take their medication for reasons other than