INTRODUCTION

Chronic myeloid leukaemia (CML) is a malignant disease, characterised by an accumulation of white blood cells in bone marrow, blood and spleen. In the past, prognosis of patients with CML was poor with median survival of around 5 years,\(^1\) which has improved dramatically by the introduction of the tyrosine kinase inhibitor (TKI) imatinib in 2001. During the last decade, four other TKIs (dasatinib, nilotinib, bosutinib and ponatinib) became available for the treatment of CML.\(^2\) Life expectancy of the majority of the patients with CML has reached that of the normal population.\(^3,4\) Although TKIs are relatively well tolerated by patients in general, its use may cause side effects.

Abstract

Objectives: To obtain insight into patients’ reasons for medication (non)adherence in chronic myeloid leukaemia (CML) and needs and wishes regarding information and communication.

Methods: A mixed-method study on the basis of a questionnaire and semi-structured interviews. The CML patient advocacy group asked patients to participate.

Results: Sixty-one patients (54 ± 12 years, 43% male) using imatinib, dasatinib or nilotinib participated. Fifteen patients (25%) reported to miss an intake at least once a month. Most were not worried about missing an intake and did not discuss missed intakes with their healthcare provider (HCP). Social activities disturbing daily routines and the wish to avoid side effects resulted in nonadherence. Patients wanted extensive and understandable information provided timely on all aspects of CML treatment, in particular on side effects, and a more supportive HCP attitude.

Conclusions: Nonadherence to CML medication does not cause concern in all patients and is not discussed pro-actively. HCP have a clear role in supporting medication adherence in CML and must be aware that social activities disturbing daily routines contribute to nonadherence. HCP should discuss (non)adherence in a direct manner, motivate patients to play an active role in managing their medication and timely provide extensive and understandable information on all aspects of CML.

Keywords
chronic myeloid leukaemia, medication adherence, medication information, patients’ experiences, qualitative research, tyrosine kinase inhibitors
effects including myelosuppression, rash, nausea, diarrhoea, fatigue, and musculoskeletal pain or myalgia. The nature and frequency of these adverse effects varies depending on the TKI.

TKI treatment is continued until progression of the disease. However, in a growing number of patients, a deep response is attained which makes discontinuation attempts feasible. Approximately 40%-60% of CML patients will remain in deep molecular remission after TKI cessation. To maximise the likelihood of achieving an optimal response, patients should be adherent to treatment. Even minor deviations from the prescribed regimen may result in poor clinical outcomes, with the probability of achieving a major molecular response being significantly better in patients with an adherence rate of at least 90%. Although measured through various methods and within different study groups, estimates of average adherence in CML vary from only 19% to almost 100% of the proportion of prescribed TKI taken.

Factors related to medication nonadherence are diverse and can be found in all five WHO-defined dimensions of adherence: social/economic factors and patient, condition, therapy, healthcare team and system-related factors. In patients with cancer, the occurrence of side effects is one of the most important factors associated with nonadherence. Higher CML complexity and regimen complexity, longer time since diagnosis, poor communication with healthcare providers (HCP), lack of knowledge and understanding of patients and lower level of social support are other factors related to nonadherence relevant in CML treatment. Patients may be intentionally or unintentionally nonadherent with the use of their medication. Intentional nonadherence is a reasoned decision-making process and occurs when the patient decides not to take medication or follow treatment recommendations. Unintentional nonadherence refers to unplanned behaviour and may be the result of forgetfulness or patients may not have understood the instructions or have difficulties with the treatment schedule. Although many data from mainly quantitative studies on factors influencing adherence are available, the reasons of patients with CML for nonadherence are still not fully understood and qualitative studies are scarce. In addition, to support patients to adhere to their medication, adequate information and communication is essential. Despite the considerable attention medication adherence has received in recent years, the provision of information remains insufficient. Care may be improved by meeting the CML patients' needs for information and communication.

The aim of this study was to obtain more in-depth insight into the patients' reasons for medication (non)adherence in CML and needs and wishes regarding information and communication. On the basis of the results, HCP may improve adherence supportive care, thereby optimising patients' drug taking behaviour.

2 | PATIENTS AND METHODS

2.1 | Study design

A mixed-method study was conducted between April 2013 and November 2015. Qualitative data were obtained by means of a short questionnaire (n = 61), and qualitative data were obtained by means of semi-structured face-to-face interviews (n = 13). The study was approved by the Medical Ethics Committee of VU University Medical Centre Amsterdam, the Netherlands (reference 2013.312).

2.2 | Patient recruitment

The study population consisted of patients with CML (≥18 years) on treatment with a TKI. The Dutch CML patient advocacy group asked 185 patients by email to participate and patients attending the annual meeting of the CML advocacy group were also asked to participate. Participating patients completed a questionnaire. Patients were asked by means of the questionnaire to participate in a semi-structured interview. Written informed consent was obtained from the interviewed patients. This study focussed on medication adherence in the implementation phase of treatment.

2.3 | Data collection

2.3.1 | Questionnaire

The questionnaire was self-composed by the researchers and included questions on basic patient characteristics (age, gender, year of diagnosis, hospital, current and past TKI treatment). Other questions addressing adherence, concerns, beliefs, side effects and information are explained below.

Adherence

Adherence was measured by means of the question: “How often do you not take your CML medicine?” to be rated as “never,” “once a month,” “twice a month” or “once a week.” Patients who indicated that they sometimes did not take their TKI, were asked to complete three additional questions concerning the reason for not taking their TKI (“forgetting,” “intentionally skipping” or “both forgetting and intentionally skipping”), whether they had concerns about not taking their TKI (“yes” or “no”), and whether they discussed not taking the TKI with their physician (“yes,” “no” or “as it comes to matter”). All patients were asked whether they used one or more reminder methods to support TKI intake.

Concerns, beliefs and side effects

Patients were asked whether they were concerned about their CML, whether they believed in the effectiveness of the TKI they used, and whether they experienced side effects. Response options were “not at all,” “somewhat,” “rather much” or “very much.”.

Information

Patients were asked about the sources they had consulted for information on TKI treatment (“physician,” “general practitioner,” “nurse,” “pharmacist,” “Internet,” “family/friends” and “other”). Patients were asked whether they were satisfied about the information provided and whether they felt sufficiently educated.
about the use of the TKI ("yes" or "no"). Patients were asked on what topics they wanted to receive more information ("the disease CML," "TKI effect," "side effects," "instructions for TKI use," "quality of life" and "other").

### 2.3.2 Interviews

An interview guide with open-ended questions was developed by the researchers and aimed to explore a rich description of the patients' experiences during CML treatment. The semi-structured interviews consisted of three parts: course of disease, patients' management of and barriers/facilitators to drug taking, and patients' needs for information and wishes with respect to communication. All interviews started with an open question about the course of disease to encourage patients to share experiences. All interviews have been performed by trained researchers at the patients' home. The interviews were digitally recorded and transcribed verbatim. The data entry was performed by the research team. All transcripts have been double checked for transcription errors by a second investigator.

### 2.4 Data analyses

#### 2.4.1 Questionnaire

Questionnaire data were analysed using SPSS version 22 for Windows (IBM Corp, Armonk, NY, USA) and described as means (standard deviation) for continuous data and as frequencies (percentages) for categorical variables. Univariate logistic regression analyses were used to determine factors associated with non-adherence ("never" versus "once a month or more"). A two-sided p-value of ≤0.05 was considered statistically significant.

#### 2.4.2 Interviews

The transcripts of the interviews were analysed using ATLAS.ti for Windows (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany). The transcripts were analysed in accordance with thematic framework analysis. This qualitative analytic method involves identifying themes based on a combination of pre-existing concepts introduced by the investigator and the themes that emerged from the data. The first phase involved familiarisation with the data through repeated and active reading of the transcripts, and by generating an initial list of issues of interest. The second phase involved the production of initial codes from the data. The first three transcripts were separately coded by a second investigator. The coding frameworks were compared and thoroughly discussed. In phase three, the different codes were combined and sorted into potential themes, and all the relevant extracts of data within the identified themes were collated. Finally, the data and themes were reviewed and refined, until associations and explanations could be drawn from the definitive concepts. Illustrative data are presented in Box 1.

### 3 RESULTS

#### 3.1 Study sample

Sixty-one patients (54 ± 12 years, 43% male) on treatment with imatinib (n = 32), dasatinib (n = 10) or nilotinib (n = 19) completed the questionnaire. Over half of the patients (33/61, 54%) used TKI as a first-line treatment, of whom most were using imatinib (29/33). Patients were treated in 28 Dutch hospitals. Thirteen patients from nine hospitals were interviewed, eight females and five males, with an age varying between 27 and 73 years. Patient characteristics are shown in Table 1 (quantitative data) and Table 2 (qualitative data).

#### 3.2 Medication adherence

##### 3.2.1 Questionnaire

Fifteen patients (25%) reported to miss an intake at least once a month (one patient twice a month) (Figure 1). Five were on treatment with imatinib (5/32, 16%), three with dasatinib (3/10, 30%) and seven with nilotinib (7/19, 37%). Reasons included forgetting (7/15), intentionally skipping (5/15) or both forgetting and intentionally skipping doses (3/15). Nine patients (9/15, 60%) reported that they had no concerns about missing an intake. Three patients

### Table 1 Characteristics of patients who filled out the questionnaire

|                        | N = 61     |
|------------------------|------------|
| **Age, years (mean ± SD)a** | 53.9 ± 11.7 |
| **Gender**             |            |
| Male                   | 26 (43)    |
| Female                 | 35 (57)    |
| **Type of hospitalb**  |            |
| Academic               | 31 (53)    |
| Nonacademic            | 27 (47)    |
| **Time since diagnosis, years (mean ±SD)c** | 6.2 ± 3.8 |
| 1-4                    | 22 (37)    |
| 5-9                    | 27 (45)    |
| ≥10                    | 11 (18)    |
| **TKI**                |            |
| Imatinib               | 32 (53)    |
| Dasatinib              | 10 (16)    |
| Nilotinib              | 19 (31)    |
| **Line of treatment**  |            |
| First-line             | 33 (54)    |
| ≥second-line           | 28 (46)    |

*aMissing data excluded from frequency analyses
**Box 1 Illustrative quotes obtained from semi-structured interviews**

**What facilitates adherence to medication?**
- It’s a kind of ritual in the evening. Brush your teeth, take off your glasses, and.. well, take your pill. Yes, it has become a ritual. I hardly ever forget them. [P9]
- I have installed an alarm on my mobile phone. The time goes by and then, oh.. it’s time to take [the pills]. Otherwise you would sit waiting, watching television, the news and then you just forget. [P2]
- During the weekend I drink two glasses of wine during dinner. I can’t drink more, because otherwise I will suffer from diarrhoea. (...) But, compared to not being there anymore.. well, then I’d rather take the pills. [P8]

**What were reasons for non-adherence to medication?**
- Sometimes it goes wrong, it goes wrong particularly on days that are different compared to usual. So for example, I have an appointment with someone at 10 o’clock and then simply forget to take my pill. [P13]
- A party is dangerous. (...) A party with a few drinks, so you get home tired. You’re not always aware of. (...) Well, often you lie in your bed and then you think, ‘hey, I have forgotten something’. [P9]
- If we go out for dinner with colleagues for example. I always take my medicines in the evening during dinner, so if I go to work and we will stay for dinner in the evening, I sometimes think ‘oh I have no medicines’ and in case I remember I will take [my medicines] in the evening when I arrive home. Sometimes I notice [the missed intake] the next day. [P3]
- Once, when I was very ill, I had fallen asleep early and the next day I felt better and I realized I didn’t take my pills. [P5]
- Well, waking up two hours before the medication intake, that doesn’t always work out. [P7]
- You think you have taken [the medication], although you actually have no idea. Or the other way around, you think you did not take them and then later you find an empty package in the trash can, which you had emptied the day before. [P7]
- Sometimes I just think, well, tomorrow I have got something, mostly something with the kids, and I think, if I had just a little bit more energy, and then I do not take the pill, or [I take] a reduced dose. [P5]
- In the beginning of October, I stopped for one week, because my muscle aches were so bad, I could not turn my head anymore. (...) So I could not drive anymore. (...) And at some point I had trouble climbing the stairs, because of the pain in my joints and my muscles. (...) Not discussed. Hey, because I was so tired, I thought, if this is how my holiday would be. [P4]
- We had a little party on Saturday evening, then you go out and you may not eat or drink anymore after 9 o’clock. Which, of course, is really annoying. (...) So, then I don’t take it, I skip it. [P6]
- I don’t expect it is noticeable in my blood (..) as long as the blood results are good, I do understand it is not smart, but, well, you get away with it, so to speak. But it makes it rather curious, thinking, how long can you skip your pills before you notice anything in your blood? [P5]
did not discuss missed doses with their physician, and five patients only discussed missed doses as it came to matter during the consult.

Twelve of the 15 nonadherent patients (80%) used the TKI as a second-line treatment or above, compared to 16 of the 46 adherent patients (35%). This difference was significant (OR: 7.50, 95% CI 1.84-30.51, P = 0.005). No relationship between the other characteristics and nonadherence was found (Table 3).

### 3.2.2 | Interview

1. **What facilitates adherence to medication?**

   Adherent patients most often reported TKI intake as part of a daily routine, being accustomed to take medication, or the use of a fixed regimen. Some patients used reminders, such as alarms or support from their partners for reminding them to take the medication. One patient used a medication box. Being aware of the importance of medication adherence, or weighing the benefits of TKI against the bothering side effects, was also reported by some patients. This stimulated them to take their pills, even at moments they would prefer not take them.

2. **What were reasons for nonadherence to medication?**

   Both unintentional nonadherence and intentional nonadherence were reported. Forgetting was the most frequent cause of unintentional nonadherence. Social activities (e.g., dining out, birthday celebration, party) disturbing daily routines contributed to forgetfulness. Some patients mentioned a variety of circumstances resulting in unintentional nonadherence. These included having no access to a liquid to swallow the medication (e.g., when driving a car), falling asleep but not yet taken the medication, or waking up too late and forgetting the medication and/or fasting regimen.
Some patients indicated that they sometimes did not remember that they had already taken the TKI, with accidentally taking too many pills as a possible consequence.

The wish to avoid or to mitigate side effects to obtain a better physical condition was the most frequent cause of intentional non-adherence. Social activities (ie children’s event, dining out, party, holiday) appeared the main underlying factor. One patient reported to have stopped TKI treatment for one week because myalgia made it impossible to participate in daily life. With respect to nilotinib, the complexity of its dosing regimen (twice daily, fasted) appeared to be a burden for patients and a factor contributing to nonadherence. In several cases, patients did not want to stay fasted, for instance when celebrating an event, and as a consequence decided to skip the intake. Also, patients sometimes forgot to stay fasted and subsequently decided not to take their medication, because of fear for an interaction with food. One patient decided to skip a dose because he was travelling to another time zone. Some patients perceived that the missed dose would have no effect on their TKI response and they argued that their haematologist also sometimes said to stop treatment for a period when experiencing side effects, or patients were aware of the possibility to discontinue TKI treatment. Some patients believed that skipping “a few pills” would not influence drug effectiveness. Illustrative data are presented in Box 1.

### 3.3 Medication beliefs

#### 3.3.1 Questionnaire

Almost all patients reported to believe in the effectiveness of their TKI: 70% “highly” and 27% “rather much.” Almost all patients reported to experience side effects: 42% “somewhat,” 42% “rather much,” and 10% “very much.” A quarter of the patients (25%) were “not at all” concerned about the CML. Most patients (72%) were “somewhat” concerned.

#### 3.3.2 Interview

Most patients were satisfied with TKI treatment and believed in the effectiveness of their medication. Positive medication beliefs included having faith in getting old, oral use at home instead of intravenous chemotherapy in the hospital, and feeling comfortable with the availability of alternative TKIs. In the course of time of treatment, patients developed more negative beliefs about TKI due to side effects (eg “nasty pills,” “a drama”). The impact of side effects on the patients’ quality of life was highlighted by the patients; it is the medication that makes them feel ill and not the disease. Patients frequently reported a combination of both positive and negative beliefs. It was described a “love-hate relationship” with their medication, or “being satisfied with the medication but looking forward to stop.” Other concerns expressed were fear of drug-drug interactions and drug-food interactions in the case of patients using nilotinib. One patient indicated to worry about the potential for harmful long-term effects of TKIs.

### 3.4 Information and communication

#### 3.4.1 Questionnaire

The physician (69%) and the Internet (59%) were the main sources consulted for information on TKI treatment. The CML patient advocacy group was not prelisted in the questionnaire but was reported by 20% of the patients. Less frequently consulted information sources were the pharmacist (3/61, 5%), nurse (2/61, 3%) and general practitioner (1/61, 2%). One patient (2%) reported to use the medication leaflet.

Most patients (87%) were satisfied about the information provided. Of eight patients (13%) who were dissatisfied, four indicated that information in general was not sufficient or not provided. One patient wanted to have more detailed information on the use of TKI, for example “can I drink coffee or tea in a fasting regimen, am I allowed to drink green tea, and am I allowed to use chewing gum.” One patient highlighted a need for more attention for severe side effects. Two patients did not report a reason. Seven (11%) patients reported not to feel sufficiently instructed about the use of TKI. The reasons included not to have received an intake schedule (n = 2) or enough detailed information (n = 1), not to have been counselled about how to fit the complex fasting regimen of nilotinib into daily life (n = 1) and how to mitigate side effects (n = 1). Four patients did not report a reason.

A total of 56 patients (92%) wanted more information on one or more topics, including side effects (67%), the disease CML (59%), TKI effect (44%), quality of life (36%) and instructions for TKI use (20%). The topic “medical advances” was not prelisted in the questionnaire but was reported by 16% of patients.

#### 3.4.2 Interview

1. What information do patients need and how should this be provided?
### TABLE 3 Univariate analysis of factors related to medication nonadherence in CML

| N = 61 | Adherent No. (%) | Nonadherent No. (%) | Univariate analysis OR (95% CI) | P    |
|--------|------------------|---------------------|---------------------------------|------|
|        |                  |                     |                                 |      |
| Age, years<sup>a</sup> |                  |                     |                                 |      |
| <50    | 15 (25.4)        | 5 (8.5)             | reference                       |      |
| 50-65  | 20 (33.9)        | 8 (13.6)            | 1.2 (0.33–4.41)                 | 0.784|
| ≥65    | 10 (16.9)        | 1 (1.7)             | 0.3 (0.03–2.97)                 | 0.303|
| Gender |                  |                     |                                 |      |
| Male   | 19 (31.1)        | 7 (11.5)            | reference                       |      |
| Female | 27 (44.3)        | 8 (13.1)            | 0.8 (0.25–2.60)                 | 0.716|
| Hospital<sup>b</sup> |                  |                     |                                 |      |
| Academic | 23 (39.7)       | 8 (13.8)            | reference                       |      |
| Peripheral | 21 (36.2)    | 6 (10.3)            | 0.8 (0.24–2.76)                 | 0.751|
| Years since diagnosis<sup>c</sup> |                  |                     |                                 |      |
| 1–4    | 20 (33.3)        | 2 (3.3)             | reference                       |      |
| ≥5     | 26 (43.3)        | 12 (20.0)           | 4.6 (0.93–23.01)                | 0.062|
| TKI    |                  |                     |                                 |      |
| Imatinib | 27 (44.3)       | 5 (8.5)             | reference                       |      |
| Nilotinib | 12 (19.7)      | 7 (11.5)            | 3.2 (0.83–11.96)                | 0.092|
| Dasatinib | 7 (11.5)       | 3 (4.9)             | 2.3 (0.44–12.11)                | 0.320|
| Line of treatment |                  |                     |                                 |      |
| First-line | 30 (49.2)      | 3 (4.9)             | reference                       |      |
| ≥second-line | 16 (26.2)    | 12 (19.7)           | 7.5 (1.84–30.51)                | 0.005<sup>*</sup>|
| Concerned |                  |                     |                                 |      |
| Not at all | 12 (19.7)      | 3 (4.9)             | reference                       |      |
| Somewhat to very much | 34 (55.7) | 12 (19.7)           | 1.4 (0.34–5.88)                 | 0.636|
| Side effects |                  |                     |                                 |      |
| Not at all to somewhat | 23 (37.7) | 6 (9.8)             | reference                       |      |
| Rather to very much | 23 (37.7) | 9 (14.8)            | 1.5 (0.46–4.90)                 | 0.502|
| Tools to prevent forgetting |              |                     |                                 |      |
| Yes | 37 (60.7)        | 13 (21.3)           | reference                       |      |
| No  | 9 (14.8)         | 2 (3.3)             | 0.6 (0.12–3.33)                 | 0.588|
| Satisfied with information |                 |                     |                                 |      |
| Yes | 41 (67.2)        | 12 (19.7)           | reference                       |      |
| No  | 5 (8.2)          | 3 (4.9)             | 2.1 (0.43–9.80)                 | 0.370|
| Sufficiently educated about TKI use |              |                     |                                 |      |
| Yes | 41 (67.2)        | 13 (3.3)            | reference                       |      |
| No  | 5 (8.2)          | 2 (3.3)             | 1.3 (0.22–7.30)                 | 0.795|
| Need for more information on: |              |                     |                                 |      |
| Side effects | 31 (50.8) | 10 (16.4)           | 1.0 (0.28–3.34)                 | 0.959|
| The disease CML | 28 (45.9) | 8 (13.1)            | 0.7 (0.23–2.38)                 | 0.607|
| Quality of life | 17 (27.9) | 5 (8.2)             | 0.9 (0.25–2.92)                 | 0.800|
| TKI effect | 20 (32.8) | 7 (11.5)            | 1.1 (0.35–3.67)                 | 0.829|
| Instructions for TKI use | 9 (14.8) | 3 (4.9)             | 1.0 (0.24–4.43)                 | 0.971|
| Medical advances | 7 (11.5) | 3 (4.9)             | 1.4 (0.31–6.24)                 | 0.665|

<sup>a</sup>Missing values excluded from analyses.

<sup>b</sup>Significant (P ≤ 0.05).
Patients expressed a wish to be counselled by a physician, preferably specialised in CML and/or working in a specialised hospital. Patients appreciated written information to take home, enabling them to re-read the information at another moment. Some patients looked for additional information on the Internet; however, they indicated being confronted with unreliable, outdated and frightening information. The Dutch CML patient advocacy group was appreciated by most patients, in particular for sharing experiences with other leukaemia patients.

There appeared a need for understandable, clear information, adjusted to the patients’ knowledge and health literacy. Some patients reported that their doctors used medical terms, which they did not understand. Patients indicated a need for accurate information, which is correct and reliable, up-to-date and not contradictory, and provided timely. Some patients reported receiving too much information, or information on other forms of leukaemia at diagnosis. Information should be honest, given directly, without scruples, telling the patient what to expect from disease and treatment.

Most patients expressed a wish for more information on side effects. Moreover, several patients indicated that information on side effects was not received, or only received at first-line treatment. When information was received, patients indicated that it was not extensive or not relevant. Patients also expressed a wish for information on impact of medicines on daily life. Patients wanted more information in advance about the frequency of hospital visits, on how to organise social support and on the possible change in sexuality. Other topics mentioned included the disease CML, TKI action and use, medical advances and experiences from other CML patients.

### 2. What do patients appreciate in HCP’s communication?

Patients indicated several attitudinal characteristics which they appreciate in their HCP: to be taken seriously, not being played down, responsible, approachable and supportive. An appropriate environment was found essential for optimal communication. Patients would like to receive the CML diagnosis face-to-face. Patients appreciated one central contact; for instance one HCP who functions as a case manager. Continuity in contact was considered of great importance. Patients wish not to have to travel long distances to see their HCP.

### 4 | DISCUSSION

The present study shows that a quarter of the CML patients was not fully adherent with medication intake. Patients using a TKI as second-line treatment or above were more likely to be nonadherent. Most of the nonadherent patients did not have worries about missing an intake, nor have they pro-actively discussed missed intakes with their physician. Social activities induced the nonadherence by disturbing daily routines or the wish to mitigate side effects to obtain a better physical condition. Patients expressed a wish for extensive and understandable information provided timely on all aspects of CML treatment, in particular on side effects. Patients expressed a need for a more supportive attitude from their HCP and continuity in contact.

The quantitative part of this study showed that 25% of the CML patients sometimes forget or skip a dose. Other quantitative studies using a questionnaire found percentages of nonadherent CML patients ranging from 0% to 47%. Differences in the extent of nonadherence in studies are a well-known phenomenon in adherence research and relate to the drug, follow-up period and differences in measurement and calculation of adherence. In the present study, a self-composed question was used to measure non-adherence (“How often do you not take your CML medicine?”). In the other studies, alternative questionnaires were used to measure medication adherence. Although the differences in measurements make it difficult to compare the results of studies, it is clear that a considerable number of CML patients have difficulties with adhering to their medication regimen.

In the present study, nonadherence was significantly associated with the use of a TKI as second-line treatment or above and, with borderline significance, a higher number of years since diagnosis. This is consistent with the results of other studies. An obvious explanation could be that in time patients have become accustomed to being chronically ill, their insecurity declines and attention fades. This may result in less precise medication intake behaviour.

It is remarkable that more than half of the nonadherent patients did not pro-actively discuss nonadherence with their physician. This could be intentionally to avoid discussion about the missed doses as patients tend to show socially desirable answers and behaviour. This may also occur unintentionally, because patients may be not aware of the consequences of the missed dose. The latter is supported by finding that a considerable number of patients stated not to worry about missed doses. In addition, it is known that certain types of feedback from HCP, that is an unaffected response and the recent advances for safe discontinuation of treatment, reinforce the unspoken opinion that missing doses is of no great importance. Patients in the present study believed that a missed dose would have no effect on their TKI response and argued that their haematologist also sometimes stops treatment for a period to mitigate side effects, or patients were aware of the possibility to discontinue TKI treatment. Patients felt unjustified reassured that “occasional” nonadherence does not matter. This has already been described in 2011 by Eliasson et al and in 2015 by Wu et al. In spite of these studies, the management of adherence is still inadequate as similar problems underlying nonadherence are still not resolved. Pro-actively addressing medication adherence by HCP is essential and should be included in daily healthcare. HCPs should ask patients whether a dose is missed, discuss the impact of nonadherence, question patients’ barriers to optimal adherence and discuss strategies to overcome them. Patients should be motivated for taking responsibility for their treatment and be made aware of their active role in managing their medication.

Social activities appeared the main underlying reason for nonadherent medication behaviour. Intentional nonadherence occurred in patients wishing to mitigate side effects to obtain a better physical
condition for a specific social activity. Unintentional nonadherence occurred when social activities disturbed the patients’ daily routines, making patients forget an intake. This is in line with the existing adherence literature.\textsuperscript{20,21,27,28} Interestingly, the most often reported facilitator for adherence in the present study was taking the medication as part of a daily routine and having become accustomed to take medication on a daily basis. This is an important cue for HCP. A frequently used intervention to support patients drug intake is alignment of drug intake with daily routines. HCP should also take the activities that disturb the daily routines into account.

Patients in the present study expressed several needs and wishes for information and communication. Side effects was the main topic patients wanted (more) information about, which is consistent with earlier studies in patients with cancer.\textsuperscript{31,44—46} Patients also expressed a wish for information on medical advances regarding CML treatment. A recent advancement in CML treatment is the possibility to discontinue treatment without loss of response.\textsuperscript{7,8,47} This opportunity, however, reinforces some patients’ nonadherence by undermining the importance of continuous correct intake. Patients should therefore be adequately educated on this topic. According to patients, information should be extensive and understandable and provided timely. Adequate provision of information has been positively related to medication adherence in CML.\textsuperscript{31,19,23,28,30,34,37} To fulfil patients’ needs for information, HCPs should provide information in a structured way and adapted to the possibilities of the individual patient to understand information and encourage patients to ask questions.

Patients expressed a need for a more supportive attitude of their HCP and continuity in contact. One central contact, which was also expressed by patients in this study, may be useful to increase supportiveness of HCP. Patients also indicated a wish not to travel long distances to see their HCP. E-health may be useful to fulfil this wish.\textsuperscript{48,49} Consultations through online video software can save travelling time for patients, while maintaining continuity of contact.\textsuperscript{50}

The strength of this study is the mixed-method study design with both quantitatively and qualitatively collected data, to provide a broad perspective and in-depth information on the subject. Potential selection bias is a limitation. Patients were approached for participation by the Dutch CML patient advocacy group. Although patients from 28 Dutch hospitals were included, caution should be used when generalising the findings to other CML patients. Patient involvement in the CML patient advocacy group may influence patient perspectives. In two interviews, the patient’s partner was present, which may have contributed to socially acceptable answers. Nine of thirteen interviewed patients used the TKI as a second-line treatment or above. A richer sample with more patients on first-line TKI treatment would provide more insights.

In conclusion, as nonadherence to CML medication does not cause concern in all patients and is not discussed pro-actively, HCP have a clear role in supporting medication adherence in CML care. An important cue is the presence of social activities as they may disturb the daily routines. Being aware of this underlying factor, discussing nonadherence directly and motivating patients to play an active role in managing their medication, will support patients’ adherence to CML medication. In addition, HCPs should provide extensive information on all aspects of CML, in a structured way and adapted to the capacities of the individual patient to understand information and encourage patients to ask questions.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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