CHAPTER 10

Summary, recommendations, and perspectives
Randomized clinical trials have demonstrated the effectiveness of oral tyrosine kinase inhibitor (TKI) treatment in improving survival in patients with chronic phase (CP) chronic myeloid leukemia (CML) [1-4]. Clinical study data show that the overall survival of CML patients achieving a major molecular response (MMR) now approaches that of the general population [5, 6]. However, although the life expectancies of optimally responding CML patients and the general population are now comparable, quality of life in patients on TKIs may be considerably reduced, due to bothersome side effects and the, in most patients, lifelong treatment duration. In addition, a significant subset of CML patients does not reach important response milestones and thereby is at risk of disease progression. Suboptimal adherence to the prescribed TKI dosing regimen plays a major role in the non-achievement of molecular responses [7]. As most CML patients use their TKI at home, they themselves are largely responsible for using their medication as prescribed. As a consequence adherence to TKI treatment is not guaranteed. The studies described in this thesis have been conducted with the aim to obtain insight into the daily clinical practice of TKI treatment in CML. In this chapter, our main findings will be discussed in the context of the current literature. Finally, recommendations are provided to optimize TKI treatment in CML patients.

MEDICATION ADHERENCE IN CML

Estimates of adherence rates of CP-CML patients vary from only 19% to almost 100% of the prescribed amount of TKI actually taken [8]. However, these rates have been measured by means of various methods, have used various definitions of adherence, and have been established in different study groups. In the RAND study (Chapter 2, 3) adherence to nilotinib was assessed by means of an electronic medication event monitoring system (MEMS), pill count, and a self-reported questionnaire (Medication Adherence Report Scale [MARS-5]). In line with the results of a recent comprehensive review comparing MEMS and non-electronic methods [9], agreement between our adherence measures was poor (Chapter 3). For each measure data are collected in a different manner and thereby different components of adherence are identified. Therefore, a combination of several methods is often used to assess medication adherence in the most optimal way [10-12]. MEMS provides detailed, objective adherence data. However, the use of this system by patients is known to influence adherence. Moreover, as the MEMS only records the opening of the container, electronic monitoring does
not provide evidence that a patient has actually taken the medication [13]. The pill count method is less interfering than the daily use of MEMS but fails to provide insight into adherence patterns [10, 11]. Subjective measures generally provide explanations for a patient’s nonadherence but responses can be biased by patients giving incorrect or false information [10, 11]. Thus, each method has its advantages and disadvantages. With regard to adherence to anticancer drugs, none of the available adherence measures will provide evidence of actual medication ingestion by a patient over a longer period of time [13]. As a result, no method is considered to be the ‘gold standard’ [10, 11]. Practical and financial barriers often also play a role in selecting the most appropriate method(s) to assess medication adherence [11]. In our study on the reasons of (non)adherence to TKI treatment (Chapter 6), only a single question was used to assess nonadherence (“How often do you not take your CML medicine?”). It was used as a means to select patients for an interview. Although this measure may be weak and biased, the single question does provide insight in the number of patients having difficulties in adhering to their medication regimen.

Several studies have shown that for imatinib an adherence rate of at least 90% is required to achieve an optimal response level [7, 14-18]. With respect to the second generation TKIs dasatinib and nilotinib, no data are available on the minimum level of adherence required to achieve an optimal response. In the RAND study protocol we hypothesized that patients experiencing a suboptimal molecular response to nilotinib would be less adherent (Chapter 2). However, although patients in this study varied greatly in their response to nilotinib (the overall 1-year MMR-rate ranged from 47-71%), they generally appeared to have a high degree of adherence to treatment with nilotinib. Therefore, it remained unclear whether a lack of adherence contributed to the lack of response (Chapter 3). The median adherence to nilotinib measured by MEMS and pill count was remarkably high with 99.0% and 99.8%, respectively, whereas an adherence rate lower than 90% was rarely observed. However, the number of patients reporting occasional nonadherence according to results obtained with MARS-5 questionnaire, increased in the first year of nilotinib treatment to a third of the patients (Chapter 3). This number of self-reported nonadherence was also found in our mixed-method study on information needs and medication adherence in CML patients using imatinib, dasatinib, or nilotinib (Chapter 6). These results are also in line with nonadherence rates found in other studies describing self-reported nonadherence of CML patients [14, 19-26]. Thus, in

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our group of patients, measured adherence was very high and we could therefore not estimate the minimal adherence rate needed to achieve an optimal response. However, a considerable number of patients clearly has difficulties in punctually adhering to their medication regimen in the long term.

**TO ADHERE OR NOT TO ADHERE**

Why some patients do and some patients do not adhere to their treatment depends on a variety of patient-, treatment-, disease-, health system-related and social factors and is influenced simultaneously by more than a single factor [8, 12, 21, 27-29]. Factors shown to have an impact on TKI adherence in CML include the choice of the TKI, convenience of its dosing regimen and duration of its use, successfullness of treatment, the occurrence and severity of side effects affecting quality of life, disease characteristics (e.g., disease severity, mental status, comorbidity and comedication), patient beliefs, education, knowledge and understanding, life style, communication with healthcare providers (HCPs) and affordability of treatment [8, 21, 27, 29]. In the present thesis, in quantitative studies, only female gender (Chapter 3), the use of a TKI (imatinib, dasatinib, nilotinib) as second (or more)-line treatment instead of first line treatment (Chapter 6), and longer treatment duration (Chapters 3, 6) were associated with nonadherence. It is likely that the small sample sizes of the studies affected the ability to assess the relationship between all potential factors and medication adherence, or limited the power necessary to detect a difference [27]. This may explain why some factors that would typically be thought to affect adherence, such as the occurrence of side effects affecting quality of life (Chapters 3, 6) and information dissatisfaction (Chapter 5), were not identified in the present thesis [27].

Qualitative research could provide a better understanding of variables affecting (non)adherence and is not dependent on statistical analyses [30]. We therefore conducted the mixed-method study described in Chapter 6, aimed to obtain an in-depth insight into the patients’ reasons for (non)adherence to CP-CML treatment. Social activities appeared the main underlying reason for nonadherent medication-taking behavior. Unintentional nonadherence may occur when these activities disrupt the patients’ daily routines and make patients forget to take scheduled doses. Intentional nonadherence may occur in patients
wishing to mitigate side effects to obtain a better physical condition for a specific social activity. The latter type of nonadherence has also been associated with the patients’ beliefs about medication [31]. CML patients often perceive taking medication not only as beneficial but also as a burden (Chapters 3, 6). These ambivalent beliefs may lead to nonadherence. In the RAND study, forgetting to take nilotinib was found to be more prevalent than intentionally skipping or adjusting a dose and was explained by the strong beliefs of the patients in the necessity of taking nilotinib (Chapter 3). On the other hand, patients’ beliefs can also be negatively influenced by certain types of feedback from HCPs as they inform patients about recent advances with respect to TKI treatment discontinuation (Chapter 6). This may cause patients to conclude that missing a dose is not a serious problem that would affect TKI responses.

NEEDS FOR INFORMATION

As mentioned above, HCPs’ actions and attitudes towards patients have a significant impact on medication adherence [8, 12, 21, 27-29]. In this respect, adequately informing patients about the disease and its treatment is absolutely essential. Patients should not only have sufficient knowledge about their disease and the way to correctly use their TKI, but also about the various effects that these drugs may bring about. Indeed, several studies have found that adequativeness of information is an important determinant of both medication adherence in CML patients [14, 21, 24, 32-36] and the successful management of TKI side effects and disease symptoms [36, 37]. In the RAND study we also investigated the relationship between information dissatisfaction and self-reported nonadherence to nilotinib. However, patient satisfaction with information on nilotinib was found to be high, which might explain why a relationship with nonadherence could not be established (Chapter 5). According to patients, improvement could be made with respect to specific information on potential problems of TKI treatment. In particular, information on the risk and management of side effects of TKIs and that TKI treatment is likely to affect various aspects of their daily lives, needs more attention (Chapters 4, 5, 6). These aspects include interference with other medication, the use of alcohol, the possible occurrence of drowsiness, and interference with the patient’s sex life. In addition, according to the interviewed patients, the information should be extensive,
understandable and should be provided timely (Chapter 6). A more supportive attitude of their HCP was appreciated, with continuity in contact (Chapter 6).

**SIMPLIFICATION OF THE NILOTINIB DOSING REGIMEN**

The twice daily, fasted intake of nilotinib is a considerable burden for CML patients. A quarter of the patients did not consistently follow the recommendations regarding the intake of nilotinib under fasting conditions (Chapter 3). With the aim of simplifying the dosing regimen and to assess potential cost reductions of TKI treatment, we investigated the effects of real-life food consumption on the pharmacokinetics (PK) of nilotinib in CP-CML patients (Chapter 7). To our knowledge the NiFo study is the first study that uses the increased absorption of nilotinib in the presence of food as a means to reduce the dose of nilotinib and improve intake conditions. In line with previous observations [38], real-life food intake substantially increased nilotinib exposure. Nilotinib PK following a reduced dose (200 mg BID) taken with a real-life meal strongly resembled that of the recommended standard dose of nilotinib (300 mg BID) taken under fasting conditions. In addition, nilotinib $C_{\text{min}}$ values were found to be higher than the minimum therapeutic target value in 95% of occasions. Clinically significant changes in ECG parameters were not observed. Supported and secured by therapeutic drug monitoring (TDM), replacement of the recommended dose under fasting conditions by a reduced nilotinib dose (200 mg BID) with a real-life meal therefore appears to be both feasible and safe (Chapter 7). The use of real-life meals, instead of standardized (high-fat) meals as used in other studies to determine the influence of food on drug absorption, must be considered a major strength of the NiFo study. Improving the intake conditions in this practical manner substantially increases the nilotinib dosing regimen’s implementability in clinical practice. Importantly, intake of a reduced dose taken with a real-life meal may also substantially reduce treatment costs. The costs of nilotinib according to the recommended dosing regimen (300 mg BID) per patient per year at official Dutch list price amount to EUR 40.000 [39]. For 250 patients this would amount to EUR 10 million per year. It is estimated that in at least 50% of the patients the nilotinib dose can safely be reduced when taken with a meal. Since the costs of nilotinib 200 mg BID per patient per year would amount to EUR 25.500 [39], adjustment of the nilotinib dosing regimen would reduce drug expenditures by about EUR 1.5 to 2 million per year.
TDM may also be useful in optimizing treatment conditions of CML patients using nilotinib according to the recommended dosing regimen [40, 41]. The mean $C_{\text{min}}$ values of nilotinib were found to be higher in patients who reported severe itching and fatigue (Chapter 3). Taking into account the high inter- and intrapatient variability of nilotinib $C_{\text{min}}$ (Chapters 3, 7), this suggests that on the basis of TDM, for some patients, a dose reduction might be considered without compromising treatment efficacy. For these patients this would mean a substantial reduction of the treatment burden. TDM-guided dose adjustment thereby would diminish the risk of treatment interruption, discontinuation, or switching due to side effects. As pointed out above, it would also reduce the costs of treatment.

**TDM ON THE BASIS OF DBS SAMPLING**

Dried blood spot (DBS) sampling is a convenient alternative to venous blood sampling as it increases the flexibility of blood level measurements required for TDM [42]. However, DBS can only be implemented in clinical practice if drug plasma concentrations determined by using DBS samples are comparable to those directly determined in venous blood samples and patients are capable and willing to perform DBS at home. For nilotinib the development and validation of DBS sampling is described in Chapter 8. Nilotinib concentrations calculated from DBS samples of capillary blood obtained by finger prick were compared with plasma concentrations in venous blood samples. DBS concentrations were lower than the corresponding plasma concentrations, which is due to the blood-to-plasma ratio of the drug. Plasma concentrations could be well predicted on the basis of DBS by correcting for the bias between plasma and DBS concentrations (Chapter 8). In Chapter 9, the feasibility of and patients’ perspective on DBS self-sampling at home was investigated. These data were obtained when performing the RAND study (Chapters 2, 3). However, 20% percent of the DBS samples collected had to be rejected because the blood spot sizes were too small for analysis. A further 3% of the samples could not be used because they did not represent a trough blood level. Interestingly, the patients who provided these samples were more often lower educated than those who provided suitable samples. The patients’ perspective on DBS self-sampling was largely positive (i.e., easy, not painful, moderate to high reliability, without additional assistance) (Chapter 9). It was preferred over venous sampling by 37% of the patients, whereas 39% had no preference. Based on the data from these two studies, we may conclude
that in clinical practice DBS sampling will be very useful in performing TDM in CML patients, but its wider application will require careful instruction. The instructions should be clear and straightforward, emphasize timing and volume of sample collection, and preferably be completed with training in practice.

METHODOLOGICAL CONSIDERATIONS

It is important to acknowledge the various methodological issues of adherence research. Adherence research demands coherent conceptualization, valid measures, appropriate analysis and complete and accurate reporting [43, 44]. In this respect, the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE) has been developed to help researchers improve the often methodologically weak or suboptimal reporting of medication adherence research [43, 44]. The guideline highlights the importance of considering and distinguishing among the three phases of medication adherence (i.e., initiation, implementation, and persistence) and describing how it is operationally defined, measured, and analyzed for each phase. Although the EMERGE guidelines were followed as much as possible (i.e., description of the adherence phase, working definition, measures and analyses), the studies of adherence described in this thesis were also subject to certain methodological issues.

Study population. It should be noted that the study population in the RAND study (Chapter 3) was heterogeneous and the number of enrolled patients limited. The study initially aimed only to include newly-diagnosed CML patients starting nilotinib treatment. However, because of poor patient accrual the protocol was amended to include all patients on nilotinib treatment, i.e., those already on treatment as well as those previously treated with another TKI. Poor patient accrual was most likely the result of CML being a rare disease and the availability of other TKIs than nilotinib for the treatment of newly-diagnosed patients, lower-priced imatinib in particular. In addition, nonadherent patients may have been less willing to participate, which may have led to an over-estimation of adherence. Unfortunately, no information was available on patient characteristics of nonparticipating patients.
**Routine care in supporting medication adherence.** No information is available on the routine clinical care related to the management of medication adherence for the study populations in this thesis. This information would help researchers to better interpret the results of the studies and is necessary to properly compare them with other studies. In the present thesis, it is unclear what adherence supporting interventions were usually provided to patients (Chapters 3, 4, 5, 6). Patients in the RAND study were highly adherent (MEMS and pill count data). Could this be the result of already adequate medication adherence management of HCPs in the hospitals participating in the RAND study? Current clinical practice of supporting TKI adherence in the Netherlands has been explored in 2014 and revealed that indeed a wide range of adherence supporting interventions is performed by HCPs, with some areas (i.e., self-efficacy, implementation) still being underexposed [45]. It is unclear whether this also accounts for the study settings in the present thesis. The “usual care in supporting TKI adherence questionnaire” may have been useful to provide this information. In addition, patients’ satisfaction with information on TKI treatment has been studied in Chapters 4 and 5. In spite of the strength of the patient-reported method to measure information on TKI treatment, it is unclear whether the information was actually provided.

**Measurement of medication adherence.** Although medication adherence is widely examined in the literature, there is no consensus on the best method of measuring it [10, 11]. In the RAND study (Chapter 3), adherence to nilotinib was assessed by means of three different methods, including at least one objective measure and one subjective measure as is recommended [10-12]. However, regarding the use of MEMS, a significant number of patients (12%) were not willing to use MEMS, because it would disturb their daily routine too much. A further 16% of the patients returned MEMS with no data, either due to MEMS malfunction or patients’ unwillingness to use the device. On the one hand, patients’ unwillingness to use MEMS may be the result of undisclosed nonadherence, which may have led to an overestimation of adherence. On the other hand, the use of MEMS may have increased the patients’ awareness of their adherence being measured. This also may have led to an overestimation of adherence. As many patients have two fixed places for storing their nilotinib capsules (one for the morning dose and one for the evening dose), the availability of two MEMS containers per patient might have been more convenient and less affective for the assessment of adherence.
In the mixed-methods study (Chapter 6) the selected adherence measure was not specifically designed to measure the extent of adherence. However, as the study focused on identifying CML patients with difficulties in adhering to their treatment, it was used as a means to select patients for an interview and to create maximal variation in the sample of CML patients.

RECOMMENDATIONS

Based on the current status of TKI use, and of nilotinib in particular, in the treatment of CML and the research described in this thesis, there is a clear need for optimizing treatment conditions. HCPs need to expand their role in supporting CML patients with their treatment. Upskilling of HCPs on the management of TKI treatment adherence and TDM dosing may be a simple and promising means to optimize current CML treatment. Recommendations for clinical practice have been described throughout this thesis and are summarized below. It would be beneficial if these recommendations are integrated in standard care.

Provide extensive information
- Provide extensive information on all aspects of CML, in a structured way and adapted to the capacities of individual patients to understand information and encourage patients to ask questions.
- Promote continuity in contact, to increase HCPs’ supportiveness.

Continuous support of CML patients to adhere to treatment
- Address medication adherence pro-actively. Ask patients whether doses are missed, discuss the impact of nonadherence, inquire about patients’ barriers to optimal adherence and discuss strategies to overcome them.
- Motivate patients to take responsibility for their treatment and make them aware that they have an active role in managing their medication.
- Promote the use of practical aids (such as alarm devices and pill boxes) which are particularly relevant to avoid unintentional nonadherence.
- Be aware that (social) activities disturbing daily routines substantially contribute to nonadherence. Support patients by taking specific action to align drug intake with their daily routines, and take into account the activities that disturb the daily routines.
Management of side effects
- Actively inquire after (perceived) side effects and how they affect a patients’ daily life, and subsequently take adequate measures to mitigate these effects.
- Support patients in correctly taking nilotinib in the absence of food to avoid potentially hazardous nilotinib plasma concentrations.

Optimize dosing by means of TDM
- Explore the use of TDM to optimize dosing in individual patients and facilitate intake with food in order to improve treatment conditions and results.
- Particularly consider the use of TDM in patients with insufficient TKI efficacy and those experiencing side effects. In the latter case, if plasma concentrations are too high, the nilotinib dose may be reduced which will improve treatment tolerability.
- Consider to use DBS self-sampling instead of venous blood sampling, to optimize patient convenience and to increase TDM applicability.

PERSPECTIVES
Successful TKI treatment should not be dependent on individual HCPs but supported by a proper multidisciplinary organization of patient care. Several HCPs are currently involved in CML care: hematologists, nurse practitioners, nurses, pharmacists, and pharmacy technicians. In line with their specialization, training in education, focus on self-management support and time spent on patient-contact, nurse practitioners appear to have the most prominent role in the management of adherence to oral anticancer drugs in Dutch clinical practice [45]. As yet, the role of pharmacists appears to be limited [45]. However, in line with their specialization as experts in the field of medicines, pharmacists (and their technicians) could attain a greater role in patient care. Multidisciplinary patient care should also include the patient and their family members. As mentioned in the recommendations for clinical practice, HCPs should motivate patients to take responsibility for their treatment and make them aware that they themselves should actively manage their medication. Multidisciplinary cooperation, adequate communication, awareness and commitment are therefore key aspects for successful TKI treatment in CML patients.
In the Netherlands, several innovative and promising initiatives aimed at improving CML care and reducing the TKI treatment burden have been introduced. One of those initiatives is CMyLife, an online platform for patients, their family members and HCPs, which facilitates patients to self-manage the care process [46]. One of its objectives is to enable a larger proportion of patients to discontinue CML treatment by optimizing medication adherence and quality of life. CMyLife connects patients and HCPs to optimize the distribution of information, support, and guidance and stimulates the innovative use of e-tools that promote healthcare at home. An example of these e-tools is MedApp. This smartphone application supports patients with their daily use of medication by means of alarms and reminders for TKI intake. It also provides an adherence pattern overview, refill reminders, a side effects tracker, and a voice recorder. In line with the results (Chapter 6) and recommendations of this thesis, MedApp (in cooperation with data science company Sentiance) continues its development by making the medication reminder service smart and adapted to the patient’s real life [47]. It would be most desirable if software would recognize when medication intake is missed and then adjust reminders accordingly, for instance when a sudden traffic jam, overwork, or social event disrupt the patient’s schedule. Another promising initiative is GLOBAS, the acronym for “Gebruik van Langdurige Orale Oncolytische Behandeling in het Albert Schweitzer (hospital [Dordrecht])”, which translates to “longterm use of oral oncolytic drugs at the Albert Schweitzer (hospital)”. This nurse practitioner-based, individualized intervention program aims to enhance medication adherence, mitigate side effects and minimalize the impact of the disease on a patients’ quality of life. The program starts with an in-depth analysis of patient characteristics and objectively assesses medication adherence by means of Real Time Medication Monitoring (RTMM). The program sets clear individual goals to be achieved by means of specific interventions and has a structured follow-up. Although this program is primarily run by the nurse practitioner, its use in clinical practice includes a multidisciplinary collaboration with hematologists, nurses, pharmacists and pharmacy technicians. RTMM can be combined with a smart reminding service for missed doses (i.e., short message service (SMS) reminders) [48]. When the RTMM device is opened, the software is updated to show that the medication was taken on time. In case the device has not been opened on schedule, patients are reminded to take their medication. A similar smart reminding and supporting system is currently evaluated in Amsterdam UMC. It comprises an interactive smartphone app (Robin) connected with a smart pill box via Bluetooth.
The interventions described above are exemplary of current developments in the use of TKI in the treatment of CML as described, among other things, in this thesis. Their practical use and effect on TKI adherence is currently evaluated. However, although on the one hand they are highly sophisticated and seem particularly promising, on the other hand it is questionable whether they will achieve a truly positive effect on adherence [8, 49]. Potentially effective intervention programs to enhance medication adherence are mostly complex with multiple components, aimed at identifying and addressing the underlying causes of nonadherence while taking into account patients’ needs and wishes. However, it has frequently been shown that the complexity of these intervention programs significantly impairs their implementability in daily practice and limits the ability to show a positive effect on adherence [8, 49]. Investigators of adherence-enhancing interventions should therefore strive for simplicity and practicality. Moreover, the often methodologically weak or suboptimal reporting of current medication adherence research should be acknowledged. As the EMERGE guidelines have been developed to improve adherence research, it is strongly recommended to follow these guidelines.

As demonstrated in the NiFo study (Chapter 7), the food-dependent bioavailability of nilotinib can be used as a means to reduce the daily dose of nilotinib and improve treatment conditions. However, as yet, no data are available on the effects of this regimen on clinical outcomes over a longer period of time in larger patient groups. Further (confirmatory) studies should therefore explore the effectiveness of nilotinib dosing together with food by establishing treatment efficacy and assessing the long-term effect on quality of life. Dosing on the basis of food-dependent bioavailability and use of DBS-based TDM according to the NiFo study model can also be applied to various other expensive oral anticancer drugs of which the bioavailability markedly improves when taken with food, but which are now taken fasted [50-52]. In addition, it would be beneficial if pharmaceutical companies would perform in-depth studies of the effects of food intake on drug exposure in relation to various ways of drug administration early in the drug development process. As the size, composition, and preparation of meals vary by country, the effects of food on the PK should include this variation in meals. In these studies, patient preferences should also be taken into account.
CONCLUSION

The present thesis not only intended to gain more insight into the daily clinical practice of CML treatment with a TKI, but also to find a number of practical means that could improve treatment conditions and thereby increase both treatment outcomes and a patients’ quality of life. In this respect, there is an urgent need to increase HCPs’ awareness of the significant impact of long-term TKI use on a patient's daily life and its consequences for adherence to TKI treatment. For a successful outcome, it is of major importance that HCPs make continuous efforts to optimize clinical practice and thereby implement a number of recommendations for improvement of standard CML care. In this regard, the following topics are of particular interest: the further optimization of dosing regimens through the use of DBS-TDM, the provision of extensive information and continuous support to CML patients to ensure full adherence with their long-term TKI treatment and the adequate management of TKI-induced side effects.
REFERENCES


