INTRODUCTION

Chronic myeloid leukemia (CML) is a malignant disease, characterized by a massive accumulation of white blood cells in bone marrow, blood and spleen and a specific chromosomal abnormality known as the Philadelphia chromosome [1]. The disease may be diagnosed at any age but is more common in middle-aged adults and appears somewhat more frequently in men than in women [2]. Up to the year 2000, prognosis of patients with CML was poor with median survival of around five years [3]. This has improved dramatically by the introduction of the tyrosine kinase inhibitor (TKI) imatinib in 2001. Consequently, the increased survival causes the prevalence of CML to rise steadily [2, 4]. In 2018 the 20-year prevalence of CML in the Netherlands has been estimated at 1983 patients [5]. In the vast majority of patients, TKIs need to be used indefinitely. In view of the increased number of patients and their long-term treatment, emphasis should be placed on the optimization of current treatment. However, to achieve this goal it is crucial to have insight into the daily clinical practice of TKI treatment in CML. Obtaining this insight has been the subject of the present thesis.

HISTORY OF CML

The first important contribution to understanding the biological basis of CML was the discovery of the Philadelphia chromosome in 1960 [6]. Peter Nowell and David Hungerford from the University of Pennsylvania in Philadelphia first described “a minute chromosome” occurring in metaphase spreads of patients with CML, later identified as an abnormally small chromosome 22 which nowadays is known as the Philadelphia chromosome. In 1973 Janet Rowley from the University of Chicago demonstrated that the Philadelphia chromosome was the result of a reciprocal translocation between chromosomes 9 and 22 (Figure 1) [7]. Later molecular techniques identified the critical genes involved: the Abelson leukemia virus (ABL) gene on chromosome 9 and the Breakpoint Cluster Region (BCR) gene on chromosome 22 [8]. Subsequently, it was shown that the BCR-ABL fusion gene encodes a constitutively activated tyrosine kinase that perturbs numerous signal transduction pathways, ultimately leading to the clinical picture of CML [1].
**Figure 1** Formation of the Philadelphia chromosome.
Parts of the normal chromosomes 9 and 22 break off and translocate in a reciprocal manner. The part of chromosome 9 (including the ABL-gene) fuses to chromosome 22 (including the BCR-gene). The newly formed chromosome 22 is called the Philadelphia chromosome, carrying the BCR-ABL fusion gene. Copyright © 2014 CML Support Group.

**DISEASE COURSE**

More than 90% of CML patients are diagnosed in chronic phase (CP) [9]. The rest of patients presents at accelerated phase (AP) or blast crisis (BC). CP CML will transform into AP and eventually BC over several years if inadequately treated. BC CML is characterized by a high number of immature blasts in the bone marrow and blood and behaves like acute myeloid leukemia [1]. In general, BC is rapidly fatal with death ensuing from bone marrow failure typically within six months.

**TREATMENT WITH TKIs**

Allogeneic stem cell transplantation (alloSCT) was the preferred treatment for patients who could tolerate the procedure and who had an available donor [10]. In case an alloSCT was not feasible, until 2000, conventional treatment consisted of nonspecific agents such as busulfan, hydroxyurea, and interferon-alfa [11]. The introduction of the TKI imatinib in 2001 however revolutionized CML treatment [12, 13]. Imatinib is an inhibitor of the constitutively active BCR-ABL tyrosine kinase. BCR-ABL positive cells show oncogene addiction and undergo apoptosis after exposure to the drug [14]. In the majority of patients, this results in the rapid clearing of Philadelphia chromosome-positive cells from the bone marrow and blood and prevents transformation to AP and BC. In around 20% of patients, response to the drug is suboptimal.
[15], which may be due to several reasons, amongst which is development of BCR-ABL ATP binding pocket mutations mediated drug-resistance [16]. Second generation TKIs like dasatinib, nilotinib and bosutinib all show preserved activity against these mutations, but remain inactive against the T315I mutation [17-20]. This mutation is only sensitive to ponatinib, a third generation TKI [21, 22].

Dasatinib and nilotinib, approved for first-line treatment of CML in 2010 [17, 18, 23, 24], have demonstrated to induce both faster and deeper molecular responses than imatinib, especially in intermediate and high-risk CML patients and therefore may be preferred for these patient groups [25, 26]. However, as yet they have not been shown to increase the survival rate [25, 26]. Bosutinib was approved for the second-line treatment of CML in 2012. Recently, following a second first-line trial [27], bosutinib was also approved for the first-line treatment of CML [19].

The choice of the first line TKI should be based on treatment goals, patient’s age, lifestyle, comorbidities, disease risk score, and side effect profiles of the drugs [20, 28, 29]. After the start of treatment, patients must be followed closely and their BCR-ABL response should be monitored every three months. Response milestones have been defined by the European Leukemia Net [28]. Patients who attain optimal response levels according to these guidelines are protected against progression to advanced phase disease. Patients who fail to respond however, need to have their TKI treatment timely adjusted in order to prevent disease progression [20, 28]. In most cases, after a change of TKI a deeper response will be obtained. However, when responses remain unsatisfactory, alloSCT may remain the only effective treatment option [28].

Remarkably, in patients who have achieved deep and long-lasting molecular responses, a trial for discontinuation of treatment can be attempted [28]. At present this is restricted to patients who have been treated with a TKI for at least three years and who have reached an MR4 (BCR-ABL ≤0.01% [International Scale]) for at least one year [29, 30]. This concerns a minority, around 25% of CML patients. TKI cessation trials showed that these attempts are successful in 40-60% of patients [30-32]. Importantly, patients with a relapse remain sensitive to TKI-retreatment with swift re-attainment of deep responses in virtually all [30-32].
Clinical study data show that the life expectancy of CML patients who respond to treatment is now close or similar to that of the general population [33, 34]. To achieve this near to normal life expectancy, most patients require lifelong treatment. Although adverse effects (AEs) of TKIs are generally mild to moderate (grade 1 or 2), including fatigue, edema, diarrhea, nausea, vomiting, abdominal pain, muscle cramps, bone and joint pain, myalgia, skin rash, itching, and headache [12, 17-19, 21, 35-37], the fact that these must be tolerated lifelong constitutes a significant burden for the patient and reduces quality of life [38-40]. There is little cross-intolerance between the separate TKIs, which enables switching to another TKI when AEs occur [41]. Unfortunately this does not hold true for the 82% of patients who are fatigued [42]. Clearly, the emotional well-being of many patients may also be affected by the occurrence of AEs [39]. Living with CML is also accompanied by a variable level of uncertainty and fear of progression [28].

**EXPOSURE-RESPONSE RELATIONSHIP OF TKIs**

Unfortunately, not all CML patients achieve adequate molecular response levels. This may be caused by resistance of leukemic cells due to the presence of mutations in the BCR-ABL kinase domain or other mechanisms [16, 43]. Response rates in CML may also be affected by pharmacokinetic factors leading to suboptimal blood levels, for example as a result of interactions with other drugs, changes in the gastrointestinal absorption and interindividual variabilities in liver (CYP3A4) metabolism and plasma-protein binding [44, 45]. Indeed, with regard to imatinib, lower trough plasma concentrations have been associated with a failure to achieve response milestones [46-48]. Similarly, lower nilotinib steady state trough plasma concentrations were associated both with a failure to achieve response milestones and a shorter time to progression in both newly-diagnosed and imatinib-resistant and imatinib-intolerant CML patients [49]. Consequently, therapeutic drug monitoring (TDM) on the basis of a target threshold concentration has been recommended [44, 45, 50].

TDM can also be used to identify potentially hazardous (supratherapeutic) TKI levels [44, 45, 50]. Major causes are medication overadherence and poor TKI metabolism [50, 51]. Supratherapeutic levels of nilotinib may also result from the concomitant intake of food,
which should be taken into account when employing TDM [52]. Several relationships between TKI plasma concentrations and toxicity have been described, proving that TDM of TKIs is important [44, 45, 50]. Higher trough plasma concentrations have been associated with the occurrence of hematological grade 3/4 adverse events and all-grade rash, diarrhea, arthralgia/myalgia, and edema (imatinib), all-grade elevations in total bilirubin and lipase levels as well as increases in QTc interval (nilotinib) and pleural effusion (dasatinib) [47, 49, 53, 54].

**MEDICATION ADHERENCE**

Interest in medication adherence has increased considerably in recent years. Awareness of the size of the problem of nonadherence has increased, as well as our knowledge of its potentially harmful clinical and economic consequences [55-57]. In 2012, international experts proposed a taxonomy for this complex and multidimensional healthcare problem [56]. Medication adherence was defined as “the process by which patients take their medications as prescribed”, divided into three phases: initiation, implementation, and persistence [56]. The process starts with initiation of treatment, when the patient should take the first dose of a prescribed medication, whereas discontinuation marks the end of treatment, when the patient stops taking the prescribed medication. The most frequently studied phase of medication adherence is implementation, defined as the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen. Persistence is the length of time between initiation and the last dose [56]. Nonadherence may occur in any of these phases and include late initiation or noninitiation, suboptimal implementation of the dosing regimen (for example, late, skipped, extra, or reduced doses or drug holidays) and early discontinuation (nonpersistence) (Figure 2) [56, 58].

Reported rates of medication adherence are variable and strongly depend on how it has been measured and expressed [55, 59, 60]. Objective methods to assess adherence include pill counts, refill data and electronic monitoring. Subjective methods include questionnaires, interviews and diaries. Studies comparing adherence measuring methods show that the type of method may influence the result obtained [59-63]. Subjective measures generally provide
explanations for a patient’s nonadherence, whereas objective measures contribute to a more precise record of a patient’s medication-taking behavior [62]. Therefore, a combination of both subjective and objective medication adherence measures is preferable to assess adherence [55, 60, 62]. In addition to measuring adherence, there are several ways to express the extent of adherence. The adherence rate describes the overall adherence during a study period and is calculated by dividing the actual use by the prescribed/intended use [64]. The Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) are somewhat similar. MPR and PDC are calculated by the number of days of medication supplied within the interval or the number of days on which the medication is available, respectively, divided by the number of days in the interval [65].

A threshold value can be used to determine the number of nonadherent patients within the population. However, there has been some debate over the cut-off point to distinguish adherence from nonadherence [55]. Traditionally a binary threshold of 80% has been used [66]. Among cancer patients a higher cut-off point of 90% or 95% is commonly used as the consequences of reduced efficacy can be serious [67, 68]. Ideally, the threshold for “good” adherence rests on clinical relevance and knowledge of dose response relations [68]. Unfortunately, for many drugs there is a lack of evidence supporting the use of a threshold value.
DETERMINANTS OF NONADHERENCE

Why some patients do and some patients do not adhere to their treatment depends on several interrelated factors. Over 150 determinants of medication adherence have been identified in earlier research [69]. According to the World Health Organization, these factors can be categorized into five dimensions: social- and economic-related factors (e.g., age, gender, education), patient-related factors (e.g., knowledge, self-efficacy and beliefs about medication), condition-related factors (e.g., disease activity, comorbidities), therapy-related factors (e.g., regimen complexity, duration of treatment, side effects), and health system/healthcare team-related factors (e.g., patient-provider relationship) [55]. Adherence to medication is influenced simultaneously by more than one factor [55]. In addition, the results of studies assessing the various factors influencing adherence are diverse and sometimes outright contradictory [70].

Nonadherence to medication can be distinguished as intentional and unintentional nonadherence [71, 72]. Intentional nonadherence is an active, reasoned decision-making process in which the patient weighs the pros and cons of treatment. It occurs when the patient decides not to take medication or follow treatment recommendations [71-73]. Unintentional nonadherence refers to unplanned behavior and may be the result of forgetfulness. Patients may also not have understood the instructions or have difficulties with the treatment schedule [71, 72]. Although this distinction is helpful, in daily practice there may be overlap of intentional and unintentional nonadherence. In addition, we should take into account the effect of particular perceptual (affective) barriers (i.e., beliefs and preferences) and practical barriers (i.e., memory barriers or daily routine barriers) that influence intentional and unintentional nonadherence [74, 75]. Intentional nonadherence is mostly due to perceptual barriers, whereas unintentional nonadherence is mostly due to practical barriers [72, 75].

MEDICATION ADHERENCE IN CML

The importance of medication adherence in CML emerged from two studies performed approximately one decade ago [76, 77]. In 2009, Noens et al. revealed that one third of patients with CML prescribed imatinib were nonadherent and that nonadherence was
associated with poorer responses to treatment [76]. Patients with a suboptimal response had significantly higher percentages of imatinib doses not taken than did those with an optimal response (23% vs. 7%, resp.). Marin et al. concluded in 2010 that medication adherence is a critical factor in achieving a molecular response [77]. MMR rates at 18 months were significantly lower for patients with an adherence rate ≤90% compared to patients with a rate >90% (9% vs. 58%, resp.). The differences in the 6-year MMR rates were even more dramatic (14% for patients with an adherence rate ≤90% vs. 94% for those with a rate >90%). The adherence rate was also correlated with the achievement of even deeper molecular responses [77]. Since then, several studies in imatinib-treated patients have been published evaluating the clinical impact of medication nonadherence in CML [78-81]. Altogether, the results of these studies show that for imatinib an adherence rate (mostly expressed by the MPR) of at least 90% is required to achieve an adequate (molecular) response as a treatment result [76-81]. As yet, no studies have been published studying the effect of (non)adherence on the clinical outcomes of other TKIs, except for a single retrospective study in 2017 [82]. This study, however, included mainly imatinib-treated patients and only a small number of dasatinib- and nilotinib-treated patients [82].

Although measured by means of various methods and within different study groups, estimates of adherence rates of CML patients vary from only 19% to almost 100% of the proportion of prescribed TKI taken [83]. Most studies on medication adherence in CML concern the use of imatinib. With respect to dasatinib and nilotinib, except for two retrospective studies in newly-diagnosed CML patients [84, 85], data on adherence to treatment with these agents are limited to those from patients receiving second-line treatment, of which eleven were retrospectively [64, 82, 86-94], two cross-sectionally [95, 96], and two prospectively obtained [97, 98]. The average adherence (expressed by either MPR or PDC) varied from 69% to 100% [82, 86-92]. No studies have been published on adherence to bosutinib or ponatinib.

As mentioned earlier for other chronic diseases, a wide variety of factors either promotes adherence to treatment, or is detrimental to it [55, 83, 95, 99, 100]. Factors shown to have an impact on adherence to TKI treatment in CML include the choice of the TKI, convenience of its dosing regimen and duration of its use, successfulness of treatment, the occurrence and severity of side effects affecting quality of life, disease characteristics (e.g., disease severity,
mental status, comorbidity and comorbidity treatment), patient beliefs, education, knowledge and understanding, life style, communication with healthcare providers (HCP) (with respect to both quality and frequency of contacts) and affordability of treatment [83, 95, 99, 100]. These factors cover all five adherence influencing dimensions set by the World Health Organization [55].

OUTLINE OF THE THESIS
The present thesis contains several studies regarding the daily clinical practice of nilotinib treatment in CML. In the vast majority of patients with CML, TKIs need to be used indefinitely. However, particularly in the case of nilotinib treatment, the necessity of a twice daily, fasted schedule is an extra burden. A better understanding of the daily clinical practice may support HCP in creating the conditions that enable CML patients to continue nilotinib treatment as long as necessary or possible in a safe and successful way while preserving the highest possible quality of life.

Chapter 1 describes the general introduction of this thesis. Chapter 2 describes the study design of the RAND study (Response and Adherence to Nilotinib in Daily Practice). This multicenter, prospective, observational study aimed to obtain insight into the daily clinical practice of nilotinib treatment in CML. Patients using nilotinib were followed for 12 months during which adherence, exposure, response to treatment, side effects, quality of life, and attitude towards CML and nilotinib use were assessed. Chapter 3 describes the results of the RAND study.

Chapters 4 and 5 present an overview of the experiences of patients with information provided by HCP on their treatment, and their characteristics regarding (dis-)satisfaction with this information. In this respect, Chapter 4 reports on the experiences of cancer patients using several oral anticancer drugs and Chapter 5 on the experiences of CML patients using nilotinib. In addition, in this chapter the relationship between information (dis)satisfaction and self-reported nonadherence to nilotinib is also described. Chapter 6 presents the results of a mixed-method study on the basis of a questionnaire and semi-structured interviews aimed to
obtain insight into reasons for medication (non)adherence given by CML patients and their needs and wishes regarding information and communication.

Chapter 7 presents the results of the NiFo study. The twice daily, fasted dosing of nilotinib is a considerable burden for CML patients. In order to simplify the dosing regimen, increase adherence and reduce treatment costs, we investigated the effects of real-life food consumption on the pharmacokinetics of nilotinib in CML patients. In the NiFo study the recommended dosing regimen (nilotinib 300 mg BID administered under fasting conditions) was compared with nilotinib at a reduced dose of 200 mg BID under ‘real-life’ fed conditions.

Nilotinib trough plasma concentrations were measured by means of dried blood spot (DBS) sampling. This convenient alternative to venous blood sampling may increase the flexibility of blood level measurements and enable TDM in daily practice. To facilitate implementability of the DBS method allowing its introduction in clinical practice, insight into the patient’s capability of DBS self-sampling at home is essential. Therefore, in Chapter 8, the development and validation of DBS sampling of nilotinib have been described. Nilotinib concentrations obtained by venous blood sampling were compared with those obtained by DBS. With the aim of clinically evaluating nilotinib plasma concentrations on the basis of DBS data, their relationship was explored. In Chapter 9, the feasibility of and patients’ perspective on DBS self-sampling at home was investigated.

Finally, in Chapter 10 the results of this thesis are summarized and discussed in the light of current literature. This chapter also provides recommendations for clinical practice and future perspectives.
REFERENCES


General introduction | 25
