Chronic Myeloid Leukemia Patients’ Adherence to Tyrosine Kinase Inhibitors in Finland: A Journey of Eighty-six Patients

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Chronic Myeloid Leukemia Patients’ Adherence to Tyrosine Kinase Inhibitors in Finland:

A Journey of Eighty-six Patients

Meri Kekäle

ACADEMIC DISSERTATION
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To All of You Who Fight for Life
Abstract

The establishment of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of chronic myeloid leukemia (CML) during the last fifteen years. This study explored the journey of 86 patients with CML using oral TKI treatment in Finland. The aim was to assess their adherence to TKIs and how the adherence, which is crucial for treatment outcomes, could be improved.

This study applied quantitative and qualitative methods and a randomized controlled study design during 2012-2014. All patients participated in the in-person interview, which followed the idea of the patient's journey with CML from the time before diagnosis to the study point. Patient-reported adherence was evaluated using Morisky's 8-Item Medication Adherence Scale (MMAS) (I-IV). Physicians were also asked to assess their patients' adherence. Patient-reported adverse drug reactions (ADRs) and quality of life (QoL) were assessed during the interview using a structured questionnaire (II, III). The patient's knowledge of the disease and TKI treatment was evaluated by asking five key questions (I, III, IV).

The intervention with 9-month follow-up in Study IV was based on tailored patient education combining nurse-conducted face-to-face counseling, educational video, patient booklet, website and text message reminders. The intervention material had the following learning objectives: CML as a disease, goals for TKI treatment, the importance of taking TKI medication as prescribed, and self-management of ADRs.

A total of 86 patients participated in the study (approximately 20% of all Finnish CML patients). Of the patients enrolled, 43 were randomized into the intervention group and 43 into the control group (IV). A total of 68 patients completed the study.

The results show that the response to TKI treatment was high (I), with 81% of the patients showing an optimal response to their treatment according to European LeukemiaNet 2013 recommendations. The CML patients’ knowledge of the disease and its treatment was poor (I). Despite the high molecular response rates to TKIs, adherence was not good in most of the patients: less than a quarter (23%) showed high adherence, 56% medium adherence, and 21% low adherence (I). Adherence was not influenced by patients’ gender, age, education, knowledge, time from diagnosis, ADRs, number of comorbidities or number of other medications. There was a considerable difference between observed and experienced adherence: 94% of the patients were highly adherent according to the physicians’ assessment, compared to 23% (I).

The most common reason for unintentional non-adherence was forgetting to take the medication (I, III, IV). In the interviews patients reported self-regulation of medication taking, particularly on those occasions where patients
wanted to avoid ADRs (III). The incidence of patient-reported ADRs was high (II). At the time of the study 97% of the patients reported suffering from at least one ADR, most commonly muscle soreness or cramp (80%), swelling of hands, legs, feet, or around the eyes (69%), and fatigue (50%).

Patient interviews indicated that ADRs were the most common barriers to adherence (III). More than half of the patients felt the ADRs had a negative influence on their daily QoL (II). Compared with the total study group, the incidences of almost all symptoms were higher among patients whose symptoms negatively affected their daily life than those who reported no such influence (II).

The patient journey model developed in the study (III) identified the following critical phases in the CML patient’s journey: getting the diagnosis, starting the treatment, getting continuous support for treatment self-management, and managing fear caused by perceived severity of the disease. Even though only 44% of the low-adherent patients in the study experienced the TKI treatment as inconvenient, most of the patients (94%) were willing to stop taking the medication in the future if possible (III).

All CML patients in the study were lacking a treatment plan and only a few had a medication list (I, III). The knowledge test (I, III) showed that patients had a poor understanding of their disease and its treatment, while low-adherent patients indicated that understanding the consequences of not taking the medication and the goal for the treatment would be motivating factors to adhere to the medication (III).

The intervention significantly improved adherence (IV). In the intervention group the MMAS score increased more often than in the control group (p=0.001). The MMAS score declined in almost half of the patients in the control group, but only in 9% of those in the intervention group (p=0.001). A majority of the patients found the intervention useful, the most useful parts being face-to-face counseling and the educational booklet. Text messages were least valued.

The findings of this study suggest that non-adherence is common among Finnish CML patients and that physicians seem to be too optimistic in assessing their patients’ adherence. The complex interplay between symptom burden, adherence, self-regulation, managing with ADRs, response to TKI therapy, and healthcare utilization highlights the need for regular symptom burden assessment in CML as a means to identify potential adherence problems before they affect the patients’ response to TKI treatment.

Tailored patient education improved the adherence of patients with CML after a 9-month follow-up. Without the additional support, adherence behavior tended to decline. Patients were most satisfied with face-to-face counseling by the nurse, which means they need personal support and practical aids to help
them manage their medication in everyday life. Access to personal counseling and information should be systematically planned as an essential part of CML care. Appropriate and updated information in printed and electronic formats should be available for nurses and other healthcare personnel to enable them to support their patients.

The findings of this study suggest that patients’ perceptions and preferences should be understood and taken into account when designing patient education interventions for real-life clinical practice. The findings also highlight the need to further evaluate the interventions to enhance adherence. There is a need for communication to increase patients’ abilities to follow their treatment plan throughout their journey, which requires real partnership between healthcare professionals and patients.
Acknowledgements

My journey with this study started in 2011 after fascinating discussions in the Department of Hematology in Turku University Hospital. “Can patients with CML from Hammersmith Hospital, London, UK, differ from Finnish patients”? I decided to find it out. During the last years the patient stories of this book have followed my personal journey to many different places around the world from Johannesburg to Singapore or ski resorts of Lapland.

First, I own my deepest gratitude to all the patients of this study who were willing to share their stories with an unfamiliar person. You will always have a special place in my heart.

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Kytäjä, June 2016

Meri Kekälä
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This thesis is based on the following original articles referred to in the text by their Roman numerals. The articles are reproduced with the kind permission of the copyright holders.


Definitions of the key concepts

Adherence
According to the World Health Organization (WHO) (2003): “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider” (Sabaté 2003).

Adverse drug reaction (ADR)
According to Edwards and Aronson (2000): “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”

Chronic myeloid leukemia (CML)
Chronic myeloid leukemia (CML) is a clonal disease of the hematopoietic stem cells in the bone marrow, which leads to a marked proliferation of granulocytes in the blood (Goldman and Melo 2003). About 20–45% of patients are asymptomatic at diagnosis and are picked up incidentally from examination of the peripheral blood. The most common clinical features include fatigue, weight loss, loss of appetite, abdominal fullness, splenomegaly, anemia, bruising and sweats (Savage et al. 1997, Faderl et al. 1999).

Morisky’s adherence scales
Morisky’s adherence scales are structured, self-reported scales for assessing medication adherence. There are two different Morisky Adherence Scales: a four-item self-reported questionnaire (Morisky et al. 1986) and an eight-item self-reported scale called the Morisky Medication Adherence Scale (MMAS) (Morisky et al. 2008).

Quality of life (QoL)
According to the World Health Organization (WHO) “individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (WHOQOL Group 1994).

Tyrosine kinases
Tyrosine kinases are enzymes that catalyze the transfer of the gamma phosphate group from adenosine triphosphate to target proteins. They play an important role in diverse normal cellular regulatory processes. Tyrosine kinases can be classified as receptor protein kinases and nonreceptor protein kinases. Receptor tyrosine kinases are transmembrane cell surface proteins that play critical roles in the transduction of extracellular signals to the
Tyrosine kinases are important mediators of the signaling cascade, determining key functions in diverse biological processes like growth, differentiation, metabolism, and apoptosis in response to external and internal stimuli. Deregulation of protein kinase activity has been shown to play a central role in the pathogenesis of human cancers (Melo and Goldman 2007). See also definition of Tyrosine kinase inhibitor.

**Tyrosine kinase inhibitor (TKI)**
A tyrosine kinase inhibitor (eg. imatinib, dasatinib or nilotinib) is a small molecular substance, which inhibits the high tyrosine kinase activity of cancer cells by inhibiting ATP or substrate binding and which directly affect the kinase activity (Melo and Goldman 2007). See also definition of Tyrosine kinases.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
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<tr>
<td>ALL</td>
<td>Acute lymphatic leukemia</td>
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<tr>
<td>alloSCT</td>
<td>Allogeneic stem cell transplantation</td>
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<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
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<tr>
<td>AML</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>ASH</td>
<td>American Society of Hematology</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>Bcr-Abl fusion gene (human)</td>
</tr>
<tr>
<td>Bcr-abl</td>
<td>Bcr-Abl fusion gene (mice)</td>
</tr>
<tr>
<td>CCyR</td>
<td>Complete cytogenetic response</td>
</tr>
<tr>
<td>CHR</td>
<td>Complete hematological response</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic myeloid leukemia</td>
</tr>
<tr>
<td>CML-AP</td>
<td>Accelerated phase of chronic myeloid leukemia</td>
</tr>
<tr>
<td>CML-BC</td>
<td>Blast crisis phase of chronic myeloid leukemia</td>
</tr>
<tr>
<td>CML-CP</td>
<td>Chronic phase of chronic myeloid leukemia</td>
</tr>
<tr>
<td>CLL</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinician reported outcome</td>
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<tr>
<td>ELN</td>
<td>European LeukemiaNet</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FACT-Leu</td>
<td>Functional assessment of cancer therapy – leukemia</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (US)</td>
</tr>
<tr>
<td>FIMEA</td>
<td>Finnish Medicines Agency</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluorescence in situ hybridization</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>IC50</td>
<td>Half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>Kela</td>
<td>Kansaneläkelaitos (Finnish Social Insurance Institution)</td>
</tr>
<tr>
<td>MDASI-CML</td>
<td>M.D. Anderson symptom inventory-CML</td>
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<tr>
<td>MEMS</td>
<td>Medication event monitoring system</td>
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<tr>
<td>MMAS</td>
<td>Morisky Medication Adherence Scale</td>
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<tr>
<td>MMR</td>
<td>Major molecular response</td>
</tr>
<tr>
<td>MPR</td>
<td>Medication possession ratio</td>
</tr>
<tr>
<td>MR3</td>
<td>Molecular response with a reduction of 3 log</td>
</tr>
<tr>
<td>MR4</td>
<td>Molecular response with a reduction of 4 log</td>
</tr>
<tr>
<td>MR4.5</td>
<td>Molecular response with a reduction of 4-5 log</td>
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<tr>
<td>MR5</td>
<td>Molecular response with a reduction of 5 log</td>
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<tr>
<td>NME</td>
<td>Negative medication experience</td>
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<tr>
<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>PAH</td>
<td>Pulmonary arterial hypertension</td>
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<tr>
<td>PAOD</td>
<td>Peripheral arterial occlusive disease</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>Ph</td>
<td>Philadelphia chromosome</td>
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<tr>
<td>Ph+</td>
<td>Philadelphia-chromosome-positive</td>
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<tr>
<td>PFS</td>
<td>Progression-free survival</td>
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<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
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<tr>
<td>QLQ-CML24</td>
<td>Quality of life module for chronic myeloid leukemia</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>qRT-PCR</td>
<td>Quantitative reverse-transcription polymerase chain reaction</td>
</tr>
<tr>
<td>QT</td>
<td>Measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle in electrocardiogram</td>
</tr>
<tr>
<td>QTc</td>
<td>Corrected QT interval</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>rIFNa</td>
<td>Recombinant interferon alpha</td>
</tr>
<tr>
<td>SCT</td>
<td>Stem cell transplantation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of product characteristics</td>
</tr>
<tr>
<td>TFR</td>
<td>Treatment-free remission</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>UMD</td>
<td>Undetectable molecular disease</td>
</tr>
<tr>
<td>URT</td>
<td>Upper respiratory tract</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1 Introduction

Chronic myeloid leukemia (CML) is a clonal disease of the hematopoietic stem cells in bone marrow, which leads to a marked proliferation of granulocytes in the blood (Goldman and Melo 2003). The annual incidence of CML in Finland and worldwide is the same, about 1 to 2 new cases per 100,000 individuals (Ruutu et al. 2002). In most cases the disease is diagnosed during further investigations of an abnormal blood count. At that time, the disease is usually in an asymptomatic chronic phase (Goldman and Melo 2003). The most common clinical features include fatigue, weight loss, loss of appetite, abdominal fullness, splenomegaly, anemia, bruising and sweats (Savage et al. 1997, Faderl et al. 1999).

Introduction of the first tyrosine kinase inhibitor (TKI), imatinib, caused a dramatic change in the management of CML more than ten years ago (Stone 2004). The prognosis of the patients improved and treatment moved from hospitals to patients’ homes. During the last five years, several second- and third-generation TKIs (dasatinib, nilotinib, bosutinib and ponatinib) have been developed, giving physicians even more options to treat CML patients. Left untreated, CML is inevitably fatal. However, the excellent results of TKI treatment (O’Brien et al. 2003, Kantarjian et al. 2012, Baccarani et al. 2013, Ross and Hughes 2014) are raising the legitimate expectation that a considerable number of patients will achieve treatment-free remission (TFR). The prevalence of patients with CML treated with TKIs is expected to increase by about 10% per year, so that CML is a challenge for healthcare systems worldwide (O’Brien et al. 2003, Storey 2009, Huang et al. 2012, Baccarani et al. 2013).

The World Health Organization (WHO) has defined adherence as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider” (Sabaté 2003). In order to achieve clinical responses in CML, medication adherence is crucial (Darkow et al. 2007). Previous studies have shown that lack of adherence to TKIs is frequent and has a significant impact on the degree of response to therapy obtained by the patient (Noens et al. 2009, Marin et al. 2010, Ibrahim et al. 2011). Marin et al. (2010) found no molecular responses when adherence was less than 80%.

For most patients, non-adherence to cancer therapy is due to several factors (e.g. treatment, patient, healthcare provider) present either at the same time or sequentially (D’Amato 2008, Doucette et al. 2012). Few previous studies have assessed CML patients’ reasons for non-adherence to TKI treatment (Eliasson et al. 2011, Efficace et al. 2012, Efficace et al. 2014). These studies have primarily focused on quantitatively investigating patient and healthcare provider characteristics that impact on adherence to TKIs in CML patients (Noens et al. 2009, Efficace et al. 2012a, Efficace et al. 2014). Patient
characteristics that have been found to affect CML patients’ adherence to TKIs are forgetfulness, patient education, knowledge and understanding, and patients’ physical and emotional feelings (Hall et al. 2016). When asked about their poor adherence to imatinib therapy, CML patients report unintentional (forgetfulness, prescribing error, drug availability) and intentional (adverse effects, social events, travel, temporary illness, negative feelings, medication taste) reasons (Eliasson et al. 2011).

Eliasson et al. (2011) found that patients who reported intentional reasons for non-adherence had greater symptom severity than patients who reported unintentional reasons. Marin et al. (2010) found significantly lower rates of adherence to imatinib among patients who reported adverse drug reactions (ADRs).

A standardized collection of health-related quality of life (QoL) data and other patient-reported outcomes (PROs) has contributed to a better understanding of overall treatment effectiveness in patients with solid tumors (Phillips et al. 2013, Trask et al. 2013), but such evidence is lacking in patients with leukemia (Aziz et al. 2011, Efficace et al. 2012b). PROs are defined by the FDA as “a measurement of any aspect of a patient’s health status that comes directly from the patient” (i.e., without the interpretation of the patient’s responses by a physician or anyone else) (FDA 2009). Documenting QoL and the adverse effects of CML treatments from the patients’ perspective is necessary to evaluate overall treatment effectiveness and the net clinical benefits of newer therapeutic strategies (Efficace et al. 2012c). A patient-centered approach to determining the symptoms most relevant to patients with CML is supported by recent findings showing that healthcare providers tend to underestimate the intensity of symptoms felt by patients with advanced cancer (Laugsand et al. 2010). While the impact of TKIs from the patient’s perspective has been little investigated, PROs could be critical for making more informed treatment decisions, as all TKIs seem to provide similar excellent clinical outcomes (Hocchaus et al. 2009, Kantarjian et al. 2012, Larson et al. 2012). More attention has been placed on understanding the impact of symptom burden on patient QoL. At the time this study was conducted, however, validated instruments to measure QoL in CML were not available or regularly used in clinical research or routine practice.

Patients with CML progress through five distinct stages in their disease experience: crisis, hope, adaptation, new normalcy, and uncertainty (Guilhot et al. 2013). Ability to cope with these stages, which could be called ‘a patient journey’, is affected by the degree of knowledge about the disease, comfort level with the physician, and optimism about the success of the treatment (Guilhot et al. 2013). Despite the work of Guilhot et al., the journey of patients with CML is not well understood. Two recent studies have focused on assessing the impact of patient-reported treatment restrictions and negative medication experiences (NMEs) on satisfaction and other health outcomes of CML patients taking TKIs (Hirji et al. 2013) and on patients’ experiences of their care, doctor-patient relationship and relationship with family and friends.
No single type of intervention is likely to be successful in improving adherence (Osterberg and Blaschke 2005, Possidente et al. 2005, D’Amato 2008). Successful interventions have been based on improving patient education and communication between patient and medical staff, simplifying medication regimens and using cues to remind patients of dosing schedules (Osterberg and Blaschke 2005). According to previous studies, using multiple interventions and different adherence aids over time may be the most successful approach (Johnson A et al. 2003, Touchette and Shapiro 2008). There is little evidence to show that educational interventions influence CML patients’ adherence to TKIs, and only one such study has previously been published (Moon et al. 2012).

This thesis concerns the journey of 86 patients with CML in Finland primarily from the perspective of adherence. The first publication concerning a high level of non-adherence to TKIs became available in 2009 (Noens et al. 2009). At that time there was no information about patients’ reasons for not adhering to TKIs. The literature provides limited information on how to improve adherence among CML patients, and there is no previous work assessing adherence from multiple viewpoints. The overall aim of this thesis is therefore to provide tools to improve the adherence and lives of patients with CML.

This thesis consists of two parts: a literature review and an empirical section. The literature review provides the contextual framework for the empirical part (Chapter 6). It covers the introduction to CML as a disease (Chapter 2), its treatments (Chapter 3), monitoring the treatment response (Chapter 3) and an overview of ADRs related to TKIs. It also describes the QoL associated with TKI treatments (Chapter 3) and the patient path in the healthcare system in Finland (Chapter 4). The world of medication adherence is evaluated in Chapter 5, which also covers current knowledge of the interventions that enhance medication adherence.

The empirical part of the thesis investigates the journey of CML patients in Finland: patients’ experience on their journey with CML, adherence to TKIs, patient-reported ADRs, and QoL (Studies I-IV). These perspectives were chosen because they are relevant for understanding the background and consequences of adherence. Currently, the literature provides no information on these subjects in Finland. Finally, the influence of tailored patient education on adherence to TKI medication among patients with CML is investigated (Study IV).
2 CML

2.1 Leukemias

Leukemia is a cancer that starts in the blood-forming cells of the bone marrow (Wetzler et al. 2005, White and Walker 2007). There are four main types of leukemia: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL) (Wetzler et al. 2005, White and Walker 2007). This thesis concentrates on patients with CML.

2.2 CML as a disease

CML is a clonal disease of the hematopoietic stem cells in the bone marrow, which leads to a marked proliferation of granulocytes in the blood (Goldman and Melo 2003). The first case of CML was described in 1845 by John Hughes Bennett and Rudolph Virchow (Bennett 1845, Virchow 1846). Myeloid leukemias (also known as myelocytic, myelogenous, or non-lymphocytic leukemias) start in early myeloid cells - the cells that become white blood cells (other than lymphocytes), red blood cells, or platelet-making cells (megakaryocytes) (Goldman and Melo 2003).

2.2.1 Philadelphia chromosome

CML differs significantly from the three other main types of leukemia: in almost all patients (95%), CML is characterized by a specific chromosome translocation known as the Philadelphia (Ph) chromosome (Nowell and Hungerford 1960, Rowley et al. 1973, Sawyers 1999). This chromosome is formed by a reciprocal translocation between the long arms of chromosomes 9 and 22 and carries a unique BCR-ABL fusion gene (Figure 1). The BCR-ABL gene encodes a constitutively active protein, tyrosine kinase. Elevated and abnormal activity of BCR-ABL tyrosine kinase leads to a massive increase in the number of myeloid cells (Druker 2008). The mechanism that leads to the formation of the Ph chromosome is unknown (Goldman and Melo 2003). The link between the Ph chromosome and CML was discovered in 1960 (Nowell and Hungerford 1960).
Chromosome 9  Chromosome 22  Philadelphia (Ph) chromosome

ABL gene + BCR gene = Fusion gene (BCR and ABL combined)

Figure 1. Reciprocal translocation between the long arms of chromosomes 9 and 22 forms the Philadelphia (Ph) chromosome, which contains the BCR-ABL fusion gene (modified from Druker 2008).

2.2.2 Three phases of CML

Clinically, without effective treatment, CML exhibits three different phases: chronic phase or CML-CP (average duration 3 to 4 years), accelerated phase (CML-AP) (average duration 6 to 9 months) and finally the blast crisis (CML-BC) (average duration 3 to 6 months) (Enright and McGlave 2000).

As the disease progresses to a more advanced phase the myeloid cells progressively lose their ability to differentiate (Druker et al. 2001). Progression of CML is related to the acquisition of additional genetic alterations probably associated with genomic instability. This can be a consequence of BCR-ABL activation or it may even represent an ancestral stem cell defect preceding the Ph-chromosome translocation, as recent observations have suggested (Melo and Goldman 2007). With current TKI therapies (see Chapter 3.2) the average rate of progression is approximately 1% per year (Druker et al. 2006, Hochhaus et al. 2009, Kantarjian et al. 2010, Saglio et al. 2010, Kantarjian et al. 2011, Kantarjian et al. 2012, Larson et al. 2012).

2.2.3 Symptoms and diagnosis

Most patients are diagnosed in the chronic phase of CML (CML-CP), which is an early, indolent stage of the disease, when 40% of patients are asymptomatic
or may experience only mild CML-related symptoms (Kantarjian et al. 1993). Therefore many patients diagnosed in CML-CP may feel physically ‘well’ for extended periods (Lee 2000). The symptoms, which may occur during the chronic phase of CML are fatigue, weight loss, loss of appetite, abdominal fullness, splenomegaly, anemia and sweats (Savage et al. 1997, Faderl et al. 1999). As CML advances to the accelerated phase and blast crisis, clinical symptoms become progressively worse (Cella et al. 2014). Patients with advanced forms of CML frequently report symptoms reflective of progressive bone marrow failure and splenomegaly, including weakness, fatigue, fevers, night sweats, weight loss, early satiety, and abdominal and bone pain (Faderl et al. 1999, Lee 2000, Hehlmann 2012). Diagnosis is fairly simple and consists of detection of the Ph chromosome abnormality or the Ph-related molecular BCR-ABL abnormalities (Jabbour and Kantarjian 2012).

2.3 Epidemiology

CML is a rare disease with an incidence of 1–2 cases per 100,000 individuals per year. It represents approximately 15% of adult leukemias (Hehlmann et al. 2007, Hoffbrand et al. 2011, Association of the Nordic Cancer Registries 2013). The overall incidence is 1.6 times higher in men than in women (Ruutu et al. 2000); this male predominance is found essentially in neonatal forms and in subjects aged 20 years and above.

The European LeukemiaNet (ELN) designed a population-based registry in 2007 to provide robust and updated information on the characteristics and epidemiology of CML (Hoffmann et al. 2015). All cases of newly diagnosed Ph-positive, BCR-ABL CML that occurred in a sample of 92.5 million adults living in 20 European countries were registered over a median period of 39 months. Almost 95% of the CML patients (n=2904) were diagnosed in the chronic phase. The median age was 56 years. More than half (56%) of the patients had comorbidities, which were mainly cardiovascular (42%). The authors concluded that from a clinical point of view the results of most trials can be generalized to most countries. The incidences observed among European countries did not differ substantially. The estimated number of new CML cases per year in Europe is about 6,370 (Hoffmann et al. 2015).

2.4 CML in Finland

Approximately 50-60 new CML cases are diagnosed in Finland every year. At the time of diagnosis the patients’ average age is 55 years (Ruutu et al. 2000). The exact number of CML patients in Finland is not known, since there is no register covering all the patients. However, most of the CML patients are on
TKI medication, which is fully reimbursed by the social insurance system, which covers the entire population (Kaikkonen et al. 2012). Reimbursements are managed by the Social Insurance Institution Kela, which is supervised by the government. In 2015 the number of CML patients receiving reimbursement for TKI treatment was more than 520 (360 received imatinib, 71 dasatinib, 90 nilotinib and <7 bosutinib and ponatinib; Figure 2) (Kela 2016). Based on this we estimate there are approximately 550 CML patients in Finland in 2016. CML medication costs Kela 15 million euros a year (Kela 2016).

![Figure 2. Number of CML patients in Finland who received reimbursed TKI medication* during 2008-2015 by Kela.](image)

*Imatinib, dasatinib or nilotinib. There were also <7 patients who received reimbursement for ponatinib or bosutinib in 2015.
3 Treatments for CML

3.1 The era before TKIs

The first pharmacotherapy reported to be active in CML was arsenic in 1865. Therapy remained palliative during most of the 1900s and included splenic irradiation, various cytostatic agents, of which busulfan was standard for almost three decades, and combination therapy (Melo and Goldman 2007). The intention of the treatment became curative with the introduction of stem cell transplantation in the 1970s (Goldman and Melo 2003). Interferon (IFN) in combination with hydroxyurea or low-dose cytarabine (ara-C) offered the prospect of prolonging survival, particularly in low-risk patients and in patients who achieve a cytogenetic remission (Hehlmann et al. 1994, Bonifazi et al. 2001).

3.2 Allogeneic stem cell transplantation

The only cure for CML is allogeneic bone marrow transplantation (alloSCT), which is not always available or effective, and in itself represents a serious risk (Faderl et al. 1999). AlloSCT is the only currently available treatment that can render patients durably molecularly negative, but the associated procedural-related morbidity and mortality are a major deterrent (Baccarani et al. 2013).

3.3 TKIs

Tyrosine kinases are important mediators of the signaling cascade, determining key roles in diverse biological processes like growth, differentiation, metabolism, and apoptosis in response to external and internal stimuli. Deregulation of protein kinase activity has been shown to play a central role in the pathogenesis of human cancers (Melo and Goldman 2007).

CML became the first neoplasia in which the elucidation of the genotype led to a rationally designed therapy of the phenotype (Melo and Godman 2007). Imatinib mesylate was the first inhibitor, which targeted the pathogenetically relevant Bcr-Abl tyrosine kinase. The invention of imatinib and other TKIs (Figure 3) has induced remissions with almost complete disappearance of any signs and symptoms of CML (Melo and Goldman 2007). This therapy has triggered an intensive search for suitable targets in other cancers and has led to the development of numerous inhibitors of potential targets now being studied in preclinical and clinical trials worldwide (Melo and Goldman 2007).
Imatinib (STI571) was called a ‘magical bullet’ when it revolutionized the treatment of CML in 2001 (Lemonick and Park 2001). Imatinib was invented in the late 1990s by biochemist Nicholas Lyndon, and its use to treat CML was driven by oncologist Brian Druker (Iqbal and Iqbal 2014). Imatinib is an adenosine triphosphate analog that selectively inhibits the enhanced tyrosine kinase activity of the Bcr-Abl oncoprotein (Figure 4) and induces durable cytogenetic responses in the majority of patients with a relatively benign ADR profile (Glivec® SPC 2015). Imatinib blocks the ATP-binding site of the BCR-ABL tyrosine kinase with high affinity and high specificity (Druker 2008). It has been found to be effective in the chronic and advanced phases of CML, as well as in blast crisis (Druker 2008).

3.3.1 Imatinib

Imatinib (Glivec®, STI571) was called a ‘magical bullet’ when it revolutionized the treatment of CML in 2001 (Lemonick and Park 2001). Imatinib was invented in the late 1990s by biochemist Nicholas Lyndon, and its use to treat CML was driven by oncologist Brian Druker (Iqbal and Iqbal 2014). Imatinib is an adenosine triphosphate analog that selectively inhibits the enhanced tyrosine kinase activity of the Bcr-Abl oncoprotein (Figure 4) and induces durable cytogenetic responses in the majority of patients with a relatively benign ADR profile (Glivec® SPC 2015). Imatinib blocks the ATP-binding site of the BCR-ABL tyrosine kinase with high affinity and high specificity (Druker 2008). It has been found to be effective in the chronic and advanced phases of CML, as well as in blast crisis (Druker 2008).
Although imatinib has been proven to be well tolerated and efficacious in the IRIS study (The International Randomized Study of Interferon and STI571) 11% of patients discontinued the treatment due to an unsatisfactory therapeutic effect within five years (Druker et al. 2006). This may be attributed to the development of resistance in these patients. In most cases, resistance is associated with the emergence of clones expressing mutant forms of BCR-ABL, which exhibit decreased sensitivity to imatinib. Another 4% of patients in the IRIS trial had to discontinue treatment with imatinib because of ADRs (Druker et al. 2006). While 87% of new patients treated with imatinib in the chronic phase achieve complete cytogenetic remission, only 29% of patients treated with this drug in the accelerated phase obtain hematological remission (Hughes et al. 2003, O’Brien et al. 2003). At >5 years, progression-free survival (PFS) ranged between 83% and 94%, and overall survival (OS) ranged between 83% and 97% (Druker et al. 2006). The number of patients still receiving initial imatinib treatment was reported at 63% to 79% after 3 to 5 years, and at 50% after 8 years (Druker et al. 2006, Deininger et al. 2009).

### 3.3.2 Second- and third generation TKIs

Head-to-head comparative clinical studies of TKI therapy in patients with CP-CML have shown that faster, deeper, and higher rates of cytogenetic and molecular responses are achievable with second- and third-generation TKIs vs. imatinib in the first-line setting (Kantarjian et al. 2012, Larson et al. 2012) and second-line setting following imatinib intolerance or resistance (Rea et al. 2012, Giles et al. 2013).
3.3.2.1 Dasatinib

Dasatinib (Sprycel®) is a piperazinyl derivative (Figure 3) that targets many tyrosine kinases and has potent inhibitory activity against the active conformation of BCR-ABL and most mutated forms (Sprycel® SPC 2015). It is indicated for first- and second-line treatment of CML (Kantarjian et al. 2010, Sprycel® SPC 2015).

The DASatinib versus Imatinib Study in treatment-naive CML patients (DASISION) study showed after 5 years follow-up, that 61% and 63% of patients randomized to receive dasatinib 100 mg once daily and imatinib 400 mg once daily, remained on treatment (Cortes et al. 2014). Major molecular response (MMR) rates by 5 years were 76% with dasatinib vs. 64% with imatinib (p=0.002), and rates of MR4.5 were 42% and 33% with dasatinib and imatinib, respectively (p=0.025)

In DASISION, 5-year rates of PFS were 85% with dasatinib vs. 86% with imatinib (Cortes et al. 2014). Similar rates of OS at 5 years were also observed with dasatinib (91%) vs. imatinib (90%) (Cortes et al. 2014).

3.3.2.2 Nilotinib

Nilotinib (Tasigna®) is a strong inhibitor of the ABL tyrosine kinase activity of oncoprotein Bcr-Abl in cell lines and in primary Ph+ leukemia cells (Weisberg et al. 2005). It is active against the wild-type Bcr-Abl gene but also against 32 of the 33 mutant forms of Bcr-Abl resistant to imatinib identified previously (Weisberg et al. 2005).

In clinical trials nilotinib has demonstrated high efficacy and good tolerability in CML patients resistant to or intolerant to imatinib, and as first-line treatment (Kantarjian et al. 2007, le Coutre et al. 2008, Saglio et al. 2010). In the 6-year follow-up of the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study patients treated with nilotinib 300 mg twice daily had significantly higher 6- year rate of MMR (77%) vs. imatinib (61%; p<0.0001) and MR4.5 (56%) vs imatinib (33%; p<0.0001) (Hughes et al. 2015).

With 6 years’ follow-up in ENESTnd, similar rates of OS were observed in the nilotinib 300-mg and imatinib arms (92 % and 91%, respectively; p=0.709). OS rate in the nilotinib 400-mg arm was higher than in the imatinib arm after 6 years’ follow-up (96% vs. 91%; p=0.0314) (Hughes et al. 2015). Follow-up of ENESTnd is ongoing and updates to survival end-points (PFS and OS) are awaited.
3.3.2.3 Bosutinib

Bosutinib (Bosulif®) is a second-generation TKI, which targets the BCR-ABL protein. Bosutinib is approved for the treatment of adult patients with CP-, AP-, and BP- Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (Bosulif® SPC 2015).

3.3.2.4 Ponatinib

Ponatinib (Iclusig®) is a third-generation TKI, which also targets the BCR-ABL protein. Ponatinib is indicated in adult patients with CP-, AP-, or BP-CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation (Iclusig® SPC 2015).

3.4 Monitoring CML treatment

European LeukemiaNet (ELN) proposed recommendations for the management of CML in 2006, 2009 and 2013 (Baccarani et al. 2013). The purpose of these guidelines is “to ensure the best possible duration and QoL for a given patient, and to avoid unnecessary complications and potentially achieve a cure, physicians and patients also must understand the proper use of available drugs, the significance of disease end points, the critical importance of monitoring, and, in some cases, the use of alloSCT as appropriate therapy” (Baccarani et al. 2013). ELN guidelines are used in CML practice in Finland.

3.4.1 Treatment goals

During the era of TKIs treatment goals have become more complex and more ambitious (Baccarani et al. 2014). Treatment goals include preventing CML from progressing to the advanced phases, attaining a survival and QoL comparable to people without CML, as well as avoiding complications and deaths related to the TKI treatment.

Treatment response in CML is measured on three different levels (Baccarani et al. 2013). The first goal is to achieve complete hematological remission (CHR) within three months of the baseline. Any patient who for any reason is not yet in CHR at 3 months must be considered a failure, mandating a change of treatment (Baccarani et al. 2014). The second goal is to achieve Ph negativity
or complete cytogenetic remission (CCyR) within 12 months of the baseline (Baccarani et al. 2013). To detect minimal residual disease, the most sensitive measure is to monitor the molecular response (MR) by measuring BCR-ABL expression (Kolibaba et al. 2013). The third goal is to achieve MMR within 18 months of the baseline (Baccarani et al. 2009). MR and CCyR are associated with good long-term outcome in patients taking imatinib (Druker et al. 2006). Achieving CCyR or MMR significantly lowers the risk of disease progression. Regular monitoring of treatment response is recommended for early detection of a loss of response or signs of disease progression (Kolibaba et al. 2013).

The response to TKI is the most important prognostic factor (Baccarani et al. 2013). ELN does not recommend which TKI should be used but which response should be achieved, irrespective of the TKI used. The responses are defined as ‘optimal’ or ‘failure’. Optimal response is associated with the best long-term outcome – a lifespan comparable with that of the general population, indicating that there is no indication for a change in that treatment. Failure means that the patient should receive a different treatment to limit the risk of progression and death. Between optimal and failure there is an intermediate zone, which was previously referred to as ‘suboptimal’ and is now designated as a ‘warning. A warning implies that the characteristics of the disease and the response to treatment require more frequent monitoring to permit timely changes in therapy in case of treatment failure (Baccarani et al. 2013).

3.4.2 Diagnostic and response monitoring methods in CML

Understanding the sensitivity of the different methods used to measure BCR-ABL is important to avoid over- and undertreatment (Baccarani et al. 2013). Three diagnostic methods are commercially available for the detection of BCR-ABL: conventional karyotypic analyses, fluorescence in situ hybridization (FISH), and quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR). Conventional cytogenetic analyses are performed on marrow aspirates, as the yield of cells in metaphase decreases significantly when peripheral blood myeloid progenitor cells are used (Baccarani et al. 2013).

The most sensitive method to detect BCR-ABL is qRT-PCR, which is a molecular test. Through amplification of the BCR-ABL mRNA transcripts, qRT-PCR is capable of detecting the presence of BCR-ABL in 1 cell out of 1 million normal cells, well below the detection level of conventional cytogenetic analysis or FISH (Hughes et al. 2006). Because of variations in standards for testing and reporting among laboratories, the International Scale was developed in 2009 to provide consistency in the interpretation of qRT-PCR results (Müller et al. 2009). Correlations between blood and marrow qRT-PCR results are excellent and therefore blood qRT-PCR is recommended for monitoring the treatment response in CML (Baccarani et al. 2013).
3.5 ADRs with TKI treatments

Recent findings show that healthcare providers tend to underestimate the intensity of symptoms felt by patients with advanced cancer (Laugsand et al. 2010). Understanding the symptom burden from the patient’s perspective could be critical for making more informed treatment decisions, as all TKIs seem to provide excellent clinical outcomes (Hocchaus et al. 2009, Larson et al. 2012, Kantarjian et al. 2012, Chapters 3.2 and 3.3). This section describes the ADRs with imatinib, dasatinib and nilotinib.

3.5.1 ADR categories

Several ADRs related to TKI therapy in CML are common to all approved TKIs, including myelosuppression, rash, nausea, diarrhea, fatigue, and musculoskeletal pain/arthralgia/myalgia, albeit occurring at varying frequencies depending on the TKI (Table 1). Nevertheless, the TKIs also have different patterns of ADRs, and this should be considered when choosing among the available molecules (Pinilla-Ibarz et al. 2015). TKI dosages in second-line therapy may be higher than in first-line therapy, and patients on second-line therapy may have more advanced disease than those on first-line therapy. Both of these factors can have a detrimental effect upon the patients’ QoL (Cella et al. 2014).

ADRs can be divided into three general categories. The first includes major, grade 3/4, ADRs that typically occur during the first phase of treatment, are manageable, but require temporary treatment discontinuation and dose reduction, and can lead to treatment discontinuation in about 10% of patients (Silver et al. 1999, Larson et al. 2012, Baccarani et al. 2013, Giles et al. 2013b, Mahon and Etienne 2014, Glivec SPC 2015, Sprycel SPC 2015, Tasigna SPC 2015).

The second category includes minor, grade 1/2, ADRs that begin early during treatment and can persist indefinitely and become chronic. They are also manageable and tolerable, but can negatively affect QoL and are a cause of decreased adherence (Pinilla-Ibarz et al. 2011, Efficace et al. 2013, Phillips et al. 2013, Efficace et al. 2014a, Glivec SPC 2015, Sprycel SPC 2015, Tasigna SPC 2015). Many of these ADRs are common to all TKIs, with some differences in frequency and severity, so that several patients can benefit from changing the TKI.

The third category includes late, so-called ‘off-target’ complications, which can affect the cardiovascular system, heart and blood vessels, the respiratory system, liver, pancreas, the immune defense, second malignancies, calcium, glucose, and lipid metabolism, etc. (Rasheed et al. 2009, Aichberger et al. 2011, Giles et al. 2013b, Kim et al. 2013). All TKIs can be toxic to the heart and
should be used with great caution in patients with heart failure. Nilotinib has been reported to be associated particularly with arterial pathology. Dasatinib has been reported to be associated particularly with pleura and lung complications. Overall, the long-term complications of second-generation TKIs are not yet fully understood and evaluable. Because these complications are a potential cause of morbidity and mortality, continued clinical monitoring of all patients is required (Pinilla-Ibarz et al. 2015).

### 3.5.2 System-specific ADRs

#### 3.5.2.1 Pulmonary ADRs

Pleural effusion is more commonly associated with dasatinib than with other TKIs (Quintás-Cardama et al. 2007). Pulmonary arterial hypertension (PAH) is observed primarily with dasatinib, most commonly in the second-line setting and in patients who previously experienced pleural effusion, suggesting a common etiology for these conditions (Quintás-Cardama et al. 2007, Rasheed et al. 2009, Irvine and Williams 2013). Prior to starting treatment with dasatinib, patients should be evaluated for PAH risk and for signs and symptoms of PAH during treatment (Sprycel SPC 2015). Dasatinib should be permanently discontinued if PAH develops on treatment (Sprycel SPC 2015).

#### 3.5.2.2 Cardiovascular ADRs

Peripheral arterial occlusive disease (PAOD; defined as atherosclerotic and thrombotic events, excluding functional, embolic, or aneurysmal disorders, in the arteries of extremities) has been described in case reports and clinical studies of nilotinib (Quintás-Cardama et al. 2007, Larson et al. 2012). PAOD has also been reported with other TKIs. In a pooled analysis of 11 clinical studies of first- or second-line dasatinib (N=2,705), 0.2% of the patients were identified as having experienced PAOD or a related event (le Coutre et al. 2013).

The QT interval is an electrocardiographic measure of ventricular depolarization and repolarization (Fradley & Moslehi 2015). Prolongation of the QT interval is associated with an increased risk of the life-threatening rhythm *torsades de pointes* and sudden cardiac death. Although the QT interval is a relatively poor predictor for the development of *torsades de pointes*, it remains an important part of oncology drug development and surveillance (Fradley & Moslehi 2015). Corrected QT interval (QTc) prolongation (QTc ≥500 ms) is rare with TKI therapy in either the first- or second-line settings, even after years of treatment (Kantarjian et al. 2010, Larson et al. 2012, Giles et al. 2013a). As indicated in the Summary of Product
Characteristics (SPC) of nilotinib and dasatinib (Sprycel SPC 2015, Tasigna SPC 2015), use of TKI therapy in CML patients with known risk factors for QT prolongation is not recommended due to potential synergistic effects.

3.5.2.3 Gastrointestinal-related ADRs

Gastrointestinal (GI)-related ADRs have been reported with all approved TKIs. In the first-line setting, GI-related ADRs were more frequent with imatinib than with either nilotinib (Saglio et al. 2010) or dasatinib (Kantarjian et al. 2010).

3.5.2.4 Laboratory abnormalities

Abnormalities in metabolic parameters have also been reported with all TKIs. Grade 3/4 elevated glucose has been reported with nilotinib (Kantarjian et al. 2011, Larson et al. 2012). Grade 3/4 hypophosphatemia occurred more frequently in the first-line setting with imatinib than with dasatinib (24% vs. 7%). In the second-line setting, grade 3/4 hypophosphatemia was reported in 17% of patients on second-line nilotinib (Kantarjian et al. 2011). In addition, chronic hypophosphatemia during TKI therapy may lead to disorders of bone mineralization, as observed in some patients on imatinib (Berman et al. 2006, Berman et al. 2013). The information on prescribing nilotinib recommends monthly monitoring of serum lipase levels and withholding therapy and adjusting dosage in cases of grade 3/4 elevated lipase or amylase (Tasigna SPC 2015).
Table 1. Frequent all-grade nonhematologic ADRs, grade 3 or 4 hematologic ADRs, and biochemical abnormalities occurring in patients with CML-CP treated with TKIs (modified from Cella et al. 2014).

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**Frequent all-grade nonhematologic ADRs, %**

- **Fluid retention**: 60 69 19 6 25 30
- **Nausea**: 50 63 11 25 10 18
- **Muscle cramps**
  - **Musculoskeletal pain**: 47 38 - - - 11 19
- **Diarrhea**: 45 48 8 12 19 27
- **Rash/skin irritation**: 40 47 41 31 11 17
- **Fatigue**: 39 48 11 21 9 24
- **Abdominal pain**: 37 32 - - - 12
- **Headache**: 37 36 14 18 13 33
- **Arthralgia**: 31 40 - - - 12
- **Nasopharyngitis**: 22 - - - - -
- **Hemorrhage**: 21 30 3 <1 5 11
- **Myalgia**: 21 20 10 11 6 13
- **Vomiting**: 17 36 5 13 5 7
- **Pyrexia**: 13 - - - - 5
- **Weight increase**: 13 32 - - - -
- **Constipation**: 9 - - 13 - 9
- **Pruritus**: 7 9 15 26 - 10

**Grade 3 or 4 hematologic AEs, %**

- **Neutropenia**: 17 36 12 31 24 35
- **Thrombocytopenia**: 9 22 10 30 19 23
- **Anemia**: 4 8 4 11 11 13

**Grade 3 or 4 biochemical abnormalities, %**

- **Elevated ALT/AST**: 5 3 4/1 4/3 <1/<1 -
- **Elevated bilirubin**: - - 4 7 1 -
- **Elevated lipase**: - - 9 18 - -
- **Hyperglycemia**: - - 7 12 - -
- **Hyponatremia**: - - - 17 7 -

-- = Not reported; ALT = alanine transaminase; AST = aspartate transaminase; URT = upper respiratory tract
3.6 QoL with TKI treatments

A standardized collection of health-related QoL data and other PROs has contributed to a better understanding of overall treatment effectiveness in patients with solid tumors (Phillips et al. 2013, Trask et al. 2013), but such evidence has been lacking in patients with leukemia (Aziz et al. 2011, Efficace et al. 2012b). PROs are defined by the FDA as “a measurement of any aspect of a patient’s health status that comes directly from the patient” (i.e., without the interpretation of the patient’s responses by a physician or anyone else) (FDA 2009). Documenting QoL and the ADRs of CML treatments from the patients’ perspective is necessary to evaluate overall treatment effectiveness and the net clinical benefits of newer therapeutic strategies (Efficace et al. 2012b). More attention has been placed on understanding the impact of symptom burden on patient QoL.

3.6.1 Instruments to assess QoL in CML

There have been few validated QoL assessment instruments specific to leukemia (Cella et al. 2014). Recently, three leukemia- and CML-specific QoL instruments have been validated: the Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) (Trask et al. 2013), the M.D. Anderson Symptom Inventory-CML (MDASI-CML) (Williams et al. 2013) and the EORTC QLQ-CML24 (Efficace et al. 2014a).

3.6.1.1 FACT-Leu

The Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) is a measure of leukemia-specific concerns in acute and chronic leukemias (Cella et al. 2012). Developed based on interviews with patients and healthcare providers and a literature search of symptoms or concerns associated with either acute or chronic leukemia, the scale comprises the 27-item FACT-G general QoL scale and a 17-item leukemia-specific subscale. The FACT-Leu includes 12 items on physical symptom concerns and five items on emotional/social concerns (Webster et al. 2002, Cella et al. 2012).

3.6.1.2 MDASI-CML

The M.D. Anderson Symptom Inventory-CML (MDASI-CML) is a multi-symptom instrument that assesses the severity of multiple symptoms and the impact of symptoms on daily functioning (Williams et al. 2013). The MDASI-CML includes 13 core symptom items, seven CML-specific symptom items, and six items on interference with daily life.
3.6.1.3 The EORTC QLQ-CML24

The EORTC QLQ-CML24 was validated in 2013 (Efficace et al. 2013). Its development was based on a literature review of health-related QoL issues relevant to CML patients together with interviews with scores of CML patients and CML experts from Europe and Taiwan (Efficace et al. 2013).

3.6.2 Effect of TKIs on QoL of patients with CML

As described in Chapter 2, CML is often diagnosed as asymptomatic in the chronic phase. It is known that even in the absence of disease symptoms negative emotional consequences can manifest (Cella et al. 2014). Efficace et al. found that CML patients younger than 59 years of age and women with CML both report more severe role limitations due to emotional problems than matched healthy controls (Efficace et al. 2011). It suggests that having CML can diminish overall QoL by affecting emotional health.

Several studies have assessed QoL of patients with CML on TKI therapy (Hahn et al. 2003, Efficace et al. 2011, Efficace et al. 2012c, Phillips et al. 2013, Trask et al. 2013). The findings are variable. In an Italian GIMEMA study CML patients on long-term imatinib therapy overall reported QoL similar to that of the general population, but younger patients with CML were more negatively affected by the disease than older patients, and women more than men (Efficace et al. 2011).

It has been found that baseline QoL and symptom burden measurements in patients with newly diagnosed CML-CP may have predictive value in terms of duration of treatment and the need for hospitalization (Cella et al. 2014). In some cases treatment with TKIs may even improve patient QoL. Patients in the IRIS study (Hahn et al. 2003) treated with imatinib reported significantly better QoL measures at each assessment than patients treated with IFN-α plus cytarabine.

The rates of dose adjustment or discontinuation due to ADRs or treatment intolerance are higher than rates of disease progression: in the IRIS study the rates of disease progression in years 5, 6, and 8 were 0.5, 0, and 0.4% respectively. In those same years of follow-up, the rates of discontinuation due to ADRs or treatment intolerance were 5, 5, and 6% (Druker et al. 2006, Deininger et al. 2009, Hocchaus et al. 2009). Therefore the symptom burden associated with TKI therapy has a greater effect on the patients’ daily life than the symptom burden of the progressive disease (Cella et al. 2014).

Studies published so far indicate that treatment with TKI therapy need not adversely affect QoL, especially if TKI-related toxicities are managed in such a way that patients can remain on therapy as directed, thereby maximizing the
likelihood of achieving better disease outcomes through significant delay of disease progression (Cella et al. 2014). ADRs are mostly mild to moderate in severity and generally consistent (i.e., predictable) over time and across lines of therapy. The number of TKIs currently approved increases the likelihood that patients found to be intolerant to one TKI can switch to another, more tolerable alternative.

### 3.7 Discontinuation of TKI treatment

In the last few years several studies have proved the feasibility and safety of imatinib discontinuation in CML. Criteria for discontinuation eligibility and for therapy resumption in cases of relapse have varied between different reports (Mahon et al. 2010, Ross et al. 2013, Rousselot et al. 2014, Mori et al. 2015). The real percentage of patients diagnosed with CML who can safely discontinue imatinib in real life has only been estimated to be 9-15% (Branford et al. 2013, Horn et al. 2013).

ELN recommends that a patient with CML who is responding optimally to TKI treatment should continue indefinitely at the standard recommended dose (Baccarani et al. 2013). The controlled discontinuations of imatinib have been attempted in some patients who were in sustained, deep MR (MR4.5 or better) (Mahon et al. 2010, Ross et al. 2013, Rousselot et al. 2014). Approximately 40% of them maintained the same degree of response during a follow-up of 1 to 4 years. Almost all of those who had a molecular recurrence regained the same level of deep response when treatment with imatinib was resumed. These data provide a proof-of-principle for the hypothesis that TKI treatment can be discontinued safely, even though some BCR-ABL cells always remain detectable (Sobrinho-Simoes et al. 2011, Chomel et al. 2011, Chu et al. 2011).

However, ELN states that data are still insufficient to make recommendations about discontinuing treatment outside of well-designed, prospective, controlled studies (Baccarani et al. 2013). TKI treatment discontinuation may be considered in individual patients, also outside studies, if proper, high quality, and certified monitoring can be ensured at monthly intervals. This is especially relevant to those fertile women who may have achieved an optimal response, because conception and pregnancy are contraindicated during TKI treatment. In these patients, when the optimal response has been stable for at least two years, TKI treatment discontinuation with or without the use of rIFNα can be considered after informed consent and with very frequent molecular monitoring (Baccarani et al. 2013).
The only CML patient-related model found from the literature is that published by Guilhot et al. (2013; Figure 6). They identified five common stages experienced by patients with CML and suggested several recommendations for healthcare professionals on the management of patients through their disease journey. By providing support, education, and reassurance, healthcare professionals can help patients as they move through the early stages of crisis and hope. When patients are in the adaptation and new-normal stages, healthcare professionals can help patients achieve and maintain a new normality by setting expectations for the risks/benefits of long-term drug therapy and disease monitoring and by continuing to support patient adherence (Guilhot et al. 2013).
Guilhot et al. showed that patients with CML progress through five distinct stages: crisis, hope, adaptation, new normalcy, and uncertainty. The ability to cope with these stages is affected by the degree of knowledge about the disease, comfort level with the physician, and optimism about the success of treatment (Guilhot et al. 2013).
There are five university hospitals and 15 central hospitals treating CML in Finland. CML is usually diagnosed by a hematologist or internist. After TKI initiation patient treatment responses are monitored in accordance with ELN Guidelines (Baccarani et al. 2013). In one hospital, patients do not meet healthcare professionals after treatment initiation and attend only for laboratory test monitoring if the treatment response is according to the guidelines. Patients are informed of the laboratory results based on each hospital’s protocol 1) by mail 2) by phone or 3) during a doctor’s appointment.

### 4.3 CML patient’s treatment path in Finland

As described in Chapter 2, the treatments for CML have developed over the decades. Nevertheless, there is little data available in the literature showing how the treatment of patients with CML is coordinated.

### 4.4 Coordinated multidisciplinary team care for CML – an ideal model?

As described in Chapter 2, the treatments for CML have developed over the decades. Nevertheless, there is little data available in the literature showing how the treatment of patients with CML is coordinated.
Holloway et al. (2012) established a team in the USA that included a hematologist, a physician assistant, and a nurse, all working closely with a social worker, a pharmacist, and a research coordinator to assist patients throughout their journey with CML. The patient and the referring community oncologist were incorporated into this team. This coordinated team care approach took advantage of each member’s specific skills to provide patients with education about CML, encourage patients’ strong involvement in tracking, monitoring results and response to therapy, and to support patients with issues that arise throughout the journey with the disease. A low rate of non-adherence with clinic visits (3%) was an indirect measure of the impact of this approach on adherence.

In an era of readily accessible information, empowering patients to participate in their care requires reliable educational materials and a good understanding of monitoring the results. In the US model, the hematologist, the first team member the patient meets on the initial visit, is an experienced leukemia specialist with expertise in all CML treatment modalities. In this model, patients are empowered through education to better understand their illness and are engaged as active team members in monitoring their responses to therapy (Holloway et al. 2012).

A multidisciplinary approach in cancer has been shown to improve patients’ adherence with treatment appointments and the treatment regimen (Boxer et al. 2011), reduce anxiety about their overall care, enhance quality of life, and improve the outcomes of certain malignancies (Gany et al. 2010, Du et al. 2011). In this US team model, the patient’s understanding of the results of response monitoring is used to tailor additional education at each subsequent clinic visit. Through frequent communication between the leukemia specialist and the referring physician, knowledge about the disease and monitoring is relayed beyond the academic medical center to community providers (Holloway et al. 2012).

Exposing the patient at each clinic visit to professional team members who deliver a consistent message throughout the course of the disease has improved relationships between patients and the team, and in some cases has improved patient adherence with clinic visits. The authors conclude that this kind of approach can help to improve overall management of CML by providing patient education, improved alliances with the healthcare team, and a good understanding of response monitoring (Holloway et al. 2012).
5 Adherence

The use of patient-administered treatments is a growing trend in oncology (Weingart et al. 2008). A patient’s ability to adhere to the requirements of their medication regime is central to the successful delivery of self-administered anticancer treatments. Research on medication adherence has been growing rapidly over the past 50 years, as chronic diseases have become more prevalent and treatment more dependent on patient self-management (Sabaté 2003). Data suggest that the difference in health outcomes between high and low adherence patients is 26%, and that the adherence–outcome relationship varies with the regimens, measurements, and diseases studied (Sabaté 2003).

This chapter describes the concept of adherence both in general and from the point of view of cancer and CML.

5.1 Definition of adherence

According to the World Health Organization, adherence is defined as “the extent to which a person’s behavior (including medication-taking) corresponds with agreed recommendations from the health care provider” (Sabaté 2003). It includes the initiation of the treatment, implementation of the prescribed regime, and discontinuation of the pharmacotherapy (Vrijens et al. 2012). The WHO has cited the problem of non-adherence with oral medications as the single most modifiable factor influencing treatment outcomes – having an even greater impact than improvements in specific medical treatments (Sabaté 2003).

‘Compliance’, a term also often used, has a different meaning (Sabaté 2003, Lehane and McCarthy 2009). Compliance describes “the extent to which the patients’ behavior (including medication-taking) coincides with medical or healthcare advice” (Sackett et al. 1978), though its meaning has become more negative regarding a patient’s behavior, since it implies passivity (Vermeire et al. 2001). In this thesis, therefore, only the term ‘adherence’ will be used.

5.2 Definition of non-adherence

There are different definitions for non-adherence (See also Chapter 5.6.1 and Table 3). In the UK CML study patients were classified as non-adherent if they had shown an adherence rate ≤90% measured using microelectronic
monitoring systems (MEMS) (Marin et al. 2010). The 90% cut-off was chosen because >90% was the level of adherence that best predicted clinical responses in their previous study (Marin et al. 2010). Investigators have also assessed adherence through self-reporting during the interviews by specifically asking patients, “It is common that patients at times miss a few doses, for a whole range of reasons. Thinking just of the past 7 days have you missed any doses?” If a patient answered ‘yes’ to this question it was taken as an indication that he/she had experienced problems with adherence (Haynes et al. 2002).

If non-adherence is defined as any deviation from the recommended treatment protocol, the problem of non-adherence becomes even more significant. Reports suggest that the proportion of patients adhering to the therapeutic regimen exactly as prescribed is as low as 19.8% (Almeida et al. 2010).

5.2.1 Definition of intentional and unintentional non-adherence

‘Intentional’ non-adherence is defined as the patient deciding to alter or discontinue the treatment, and ‘unintentional’ non-adherence as the patient intending to take the medication as prescribed, but being unable to do so (Horne et al. 2002, Nunes et al. 2009). Intentional non-adherence can happen even when patients are fully aware of the risks and consequences of not taking their medications as prescribed. For instance, one factor that could contribute to intentional adherence is ADRs experienced by the patient. Unintentional non-adherence occurs when a patient is willing to follow the agreed treatment but fails to do so due to factors beyond their control. A patient can, for example, forget to take the prescribed medication, misunderstand the instructions, be unable to pay for the treatment, or have difficulties in administering the medication; it may also be due to a prescribing error (Eliasson et al. 2011, Gadkari and McHorney 2012).

5.3 Methods to measure adherence

Adherence represents a range of behaviors from taking all medication as prescribed to an occasionally skipped dose and taking few or no doses at all (Osterberg and Blaschke 2005). Different tools have been used to evaluate and assess patients’ adherence to medication, and there is no “gold standard” measure of medication adherence.

The methods used to monitor medication adherence are either direct or indirect and include self-reporting, frequency of repeat prescriptions, pill counts, drug plasma levels, and various microelectronic monitoring systems (Sabaté 2003, Osterberg and Blaschke 2005, Ruddy et al. 2009; Table 2). Self-
reporting is probably the most frequently used method, but it is often biased because many patients overestimate their medication adherence (Partridge et al. 2002).

Monitoring of drug or metabolite concentrations may be one of the more accurate ways to measure adherence, but this method has its own challenges in that it is only applicable to certain drugs, and it may not account for individual variation in the metabolism of the drug (Lam and Fresco 2015). Concentration monitoring may not be practical or financially feasible for most patients (Partridge et al. 2002). Additionally, the data for many anticancer medications are insufficient to recommend routine therapeutic drug monitoring in clinical practice.

Although several different approaches have been used to assess medication adherence, the issue still remains as to what cut-off should be used to define adequate adherence (Nieuwlaat et al. 2014). The literature is conflicting regarding what percentage of doses taken should be used to define adherence, and many studies use a range of 80–95% (Partridge et al. 2002, Osterberg and Blaschke 2005). Little evidence is available to support these values, and the percentage desired may vary depending on the medication prescribed and the corresponding disease state (McCue et al. 2014).

<table>
<thead>
<tr>
<th>Method</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug or metabolite concentrations</td>
<td>Objective; high level accuracy</td>
<td>Not applicable to all medications; does not account for pharmacogenomics; expensive</td>
</tr>
<tr>
<td>Microelectronic monitoring</td>
<td>Precise; quantitative</td>
<td>Expensive; mostly used in clinical trials; does not track ingestion of medication</td>
</tr>
<tr>
<td>Pill counts</td>
<td>Objective; quantitative; easy to perform</td>
<td>Easily altered by patient; does not account for adherence to schedule</td>
</tr>
<tr>
<td>Prescription refill history</td>
<td>Objective; easy to obtain data</td>
<td>Does not account for adherence to schedule</td>
</tr>
<tr>
<td>Self-reporting</td>
<td>Simple; inexpensive; useful in clinical setting</td>
<td>Often overestimated and subject to patient bias</td>
</tr>
</tbody>
</table>
5.3.1 Self-reported questionnaires

Standardized, self-reported questionnaires have frequently been used because they are low in both cost and time expenditure. Early studies found that the self-report method underestimated non-adherence when compared with pill counts or biological assays (Saini et al. 2009, Moore and Brandt 2010). However, subsequent research suggests that the self-report method may provide a reasonably accurate estimate of adherence (Grunfeld et al. 2005, Hershman et al. 2010). Such questionnaires, validated by more objective measures, may also be useful in identifying patients who may benefit from intervention.

5.3.1.1 Morisky scales

Among structured, self-reported scales, a four-item self-reported questionnaire to assess medication adherence was developed by Morisky et al. (1986). Although the four-item scale has shown poor psychometric properties, it is one of the most widely used self-reported measures of medication adherence (Shalansky et al. 2004). It has been used in two published CML adherence studies (Efficace et al. 2012, de Almeida et al. 2013).

An eight-item self-reported scale called the Morisky Medication Adherence Scale (MMAS) was developed by Morisky et al. in 2008 (Appendix 1). MMAS is a structured questionnaire validated to estimate adherence to treatment and is widely used in chronic diseases (Morisky et al. 2008). The 8-item scale consists of seven questions with ‘yes’ or ‘no’ alternatives and one item (the last one) with a 5-point Likert scale. MMAS evaluates items addressing the circumstances surrounding adherence behavior. Each item measures a specific medication-taking behavior and not a determinant of adherence behavior. MMAS scores can range from 0 to 8 and have been classified into three levels of adherence: high adherence (score 8), medium adherence (score 6 to 7.75) and low adherence (score <6) (Morisky et al. 2008).

5.3.1.2 French self-assessment CML questionnaire

Daouphars et al. (2013) have recently developed a self-assessment questionnaire consisting of 10 questions to identify patients who were not adhering to their cancer treatment. Each answer was worth 1 point, resulting in a possible maximum score of 10. The questionnaire was validated in patients receiving imatinib, using an objective adherence evaluation: a patient’s score on the self-assessment questionnaire was correlated with prescription refills, expressed as a medication possession ratio. A score of less than 8 was associated with a positive predictive value of 0.83 to have a medication possession ratio below 90%. Using this questionnaire, half of the patients receiving imatinib would be identified as being non-adherent (sensitivity 0.5).
Few adherent patients would be falsely identified as non-adherent, as the questionnaire’s specificity was 0.97 (Daouphars et al. 2013).

5.3.2 MEMS

The Medication Event Monitoring system (MEMS) consists of electronic detection of package entry by incorporating a microcircuit into pharmaceutical packages of various designs, which detects, time-stamps, and stores the maneuvers needed to remove a drug dose (Vrijens and Urquhart 2014). This automatic compilation of times of medication intake (dosing history) provides a thorough characterization of medication adherence, with clear distinctions between initiation, implementation and discontinuation (Vrijens and Urquhart 2014). However, opening the medication package does not necessarily correlate with administration of the medication and can be manipulated by the patient. This system is also expensive and therefore may not be a feasible option within the community setting (Ruddy et al. 2005).

MEMS is an indirect method of estimating when the drug is administered and how much, but it has been shown to give a good prediction of drug concentration in plasma (Vrijens and Urquhart 2014). Electronic monitoring of package entry is the current gold standard for automatically compiling drug dosing in trial settings (Vrijens and Urquhart 2014). It has been used in more than 700 peer-reviewed publications (Lam and Fresco 2015).

Alili et al. (2016) found in their recent scoping review, that when MEMS was compared to non-electronic methods, the median adherence per method was overestimated by 17% (range: -21%, 75%) for self-report, 8% (-25%,50%) for pill count and 6% (-15%,50%) for rating.

5.3.3 Pill count

Pill count is an indirect, objective measure that counts the number of dosage units that have been taken between two scheduled appointments or clinic visits. This number would then be compared with the total number of units received by the patient to calculate the adherence ratio (Farmer 1999, Vik et al. 2004). The low cost and simplicity of this method contribute to its popularity.

Adherence underestimation occurs frequently, since this method simply uses the dispensed date as the denominator of the equation without considering the chance of having surplus medication (Lam and Fresco 2015). It is common for patients with chronic conditions, in particular, to replenish their medication before it runs out (Vik et al. 2004). The cut-off value to differentiate between adherence and non-adherence, in this case, is generated arbitrarily (Farmer 1999).
Even though pill count is based on a similar assumption to MEMS, i.e. that removal of the dosage unit is equivalent to taking the medication, pill count does not generate a medication-taking pattern like MEMS does (Lam and Fresco 2015). Removing the correct number of dosage units from the container does not necessarily mean the patient follows the dosing regime consistently (van Onzenoort et al. 2010). Besides pill count’s inability to characterize the adherence pattern, it is also unable to identify its causes (Farmer 1999).

Pill count has shown higher accuracy compared to other subjective methods, but MEMS has replaced pill count as a reference standard for validating other adherence measures in the 1990’s (Farmer 1999).

5.4 Physician’s assessment

It has been documented in the literature that physicians are inaccurate estimators of adherence and are “no better than chance” at judging which patients are adherent and which are not (Wagner et al. 2001, Zeller et al. 2008). When estimating the degree of adherence for any particular patient, physicians have been shown to be accurate only 10–40% of the time, for both medication and other treatments (Turner et al. 2001, Parker et al. 2007, Morton et al. 2008). Improving non-adherence detection by physicians has the potential to directly increase patients’ treatment adherence and improve patients’ health outcomes (Phillips et al. 2011).

Phillips et al. found several factors related to physicians’ adherence predictions, including physicians’ perceptions of patient agreement regarding treatment. The degree to which physicians discussed treatment specifics with the patient moderated agreement perception accuracy but not adherence prediction accuracy.

Little is presented in the literature about how physicians estimate their CML patients’ adherence to TKI therapies. In the Belgian ADAGIO study, physician-investigators were asked to estimate the percentages of patients adhering to imatinib treatment in the first month after diagnosis and after one year (Noens et al. 2009). The physicians in that study believed that on average 92.8% of patients were imatinib adherent in the first month after diagnosis and 87.4% after one year of treatment.
5.5 Adherence in cancer

The adherence rates to oral anticancer therapies vary greatly; for example, a review of six studies investigating adherence to oral anticancer treatments in adults reported non-adherence rates between 0% and 83% (Partridge et al. 2002). This variation in reported non-adherence rates can be partly explained by differences in methods and measurements and by definitions of non-adherence. The average non-adherence rate to oral anticancer treatments has been estimated as 21% (DiMatteo 2004).

Patients with breast cancer are the most studied population with regard to how well they adhere to oral cancer therapy. A recent systematic review of the use of adjuvant hormonal therapy in clinical practice showed that adherence over periods longer than four years ranged from 41% to 72%, while the rate of discontinuation ranged from 31% to 73%, measured after five years of therapy (Murphy et al. 2012). Adherence to other oral therapies used in the treatment of breast cancer has been reported to be higher than that measured with hormonal therapies (Mayer et al. 2009, Partridge et al. 2010, Ruddy et al. 2012). It is unclear whether this variation is due to differences in methodology, treatment plan, breast cancer status, or a combination of these factors.

5.6 Adherence in CML

5.6.1 Adherence rate in CML


Variation in definitions of adherence makes it difficult to gain an accurate estimate of the rate of medication adherence in patients with CML. Most studies report the level of non-adherent behavior in a proportion of CML patients. Of those studies providing data on the number of patients who were fully or 100% adherent (Almeida et al. 2010, Guerin et al. 2010, Wu et al. 2011,
Efficace et al. 2012a), very few patients met these criteria, with rates ranging from 20% (Almeida et al. 2010) to 53% (Guilhot et al. 2010). When the mean adherence rates were provided, patients’ level of adherence ranged from 76% (Feng et al. 2006) to 98% (Casamartina et al. 2010, Ibrahim et al. 2010, Marin et al. 2010a, Marin et al. 2010b, Koren-Michowitz et al. 2012).

5.6.2 Factors affecting adherence of patients with CML


![Diagram of non-adherence factors](Image)

*Figure 7. Model of non-adherence (adapted from Ruddy et al. 2009, Jabbour et al. 2012).*
### Table 3. The methods of measuring adherence to TKIs in CML (Gater et al 2012).

<table>
<thead>
<tr>
<th>Measurement tool</th>
<th>Adherence calculation</th>
<th>Adherence definition</th>
</tr>
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<tbody>
<tr>
<td><strong>1) Monitoring systems</strong>&lt;br&gt;MEMS</td>
<td>Dose taken according to the MEMS reading expressed as a percentage of the dose prescribed during the total duration of the study</td>
<td>*Definition of adherence according to MEMS not provided&lt;br&gt;*Non-adherence defined as ≤90% as measured by MEMS (90% cut-off chosen as it was the level of adherence that best predicted clinical responses in a previous clinical study)</td>
</tr>
<tr>
<td><strong>2) Manual monitoring</strong>&lt;br&gt;a) Pill count</td>
<td>Percentage of imatinib taken to imatinib prescribed</td>
<td>*Definition of adherence not provided</td>
</tr>
<tr>
<td>b) Adherence with scheduled appointments</td>
<td>Ratio of appointments scheduled to appointments kept Dose interruptions of more than one-week due to non-attendance at scheduled appointments</td>
<td>*Definition of adherence not provided</td>
</tr>
<tr>
<td><strong>3) Medication possession</strong>&lt;br&gt;a) Medication possession ratio (MPR)</td>
<td>Total days' dose of TKI divided by number of days in the observation time</td>
<td>*Definition of adherence according to MPR not provided&lt;br&gt;*Low MPR (non-adherence) defined as &lt;85% (85% threshold chosen as it is midpoint of previous thresholds in cancer research) *Good (≥90%); medium (70–89.9%); poor (&lt;70%)&lt;br&gt;*Low (&lt;65%); medium (65–95%); high (95–100%)</td>
</tr>
<tr>
<td>b) Treatment possession ratio</td>
<td>[total dose of treatment obtained at pharmacy]/[total dose of treatment prescribed at hospital during the same period]</td>
<td>*Definition of adherence not provided</td>
</tr>
<tr>
<td>c) Daily average consumption</td>
<td>[Total mgs dispensed]/[Total days supply]</td>
<td>*Definition of adherence not provided</td>
</tr>
<tr>
<td>d) Treatment discontinuation</td>
<td>Continuous days of non-treatment</td>
<td>*Gap &gt; 20 days due to non-adherence *Gap ≥ 30 days</td>
</tr>
<tr>
<td><strong>4) Medication claims</strong>&lt;br&gt;a) Proportion of days covered</td>
<td>[Days of supply for claims of the index drug]/[total number of calendar days in the study period (i.e. up to 6 months after the index date)]</td>
<td>*Definition of adherence not provided</td>
</tr>
<tr>
<td><strong>5) Clinician reported outcome (CRO)</strong>&lt;br&gt;a) Basel Assessment of Adherence Scale with immunosuppressive medication</td>
<td>4-Question clinical interview guide, used with patients and carers</td>
<td>*Non-adherence: positive answer to any question&lt;br&gt;*Definition of adherence not provided</td>
</tr>
<tr>
<td>b) Visual analogue scale (VAS)</td>
<td>Rating of patient adherence on 10 cm VAS scale (physician, patient and carer rating)</td>
<td></td>
</tr>
<tr>
<td><strong>6) Patient reported outcome (PRO)</strong>&lt;br&gt;a) Qualitative patient interviews</td>
<td>Patient self-report question: &quot;It is common that patients at times miss a few doses, for a whole range of reasons. Thinking of the past 7 days have you missed any doses?&quot;</td>
<td>*If a patient answered ‘yes’ it was taken as an indication that patient had problems with adherence.</td>
</tr>
<tr>
<td>b) Visual analogue scale (VAS)</td>
<td>Rating of patient adherence on 10 cm VAS scale (physician, patient and carer rating)</td>
<td>'Intentional' non-adherence: patient deciding to alter or discontinue the treatment. 'Unintentional' non-adherence: patient intending to take medication as prescribed, but unable to do so *Definition of adherence not provided</td>
</tr>
<tr>
<td><strong>7) Combined CRO/PRO assessment</strong>&lt;br&gt;a) CML-Q</td>
<td>Specific questions asking about compliance to medications (How often miss medications)</td>
<td>*‘True-compliance’ (patient-perceived and physician-perceived compliant) or ‘non-compliance’ (reported non-compliant by patient, physician or both)</td>
</tr>
</tbody>
</table>
In order to better understand the complex factors that influence patients’ adherence to TKIs, Gater et al. (2012) have developed a conceptual model of adherence to peroral TKIs for the treatment of CML (Figure 8).

This model consists of four different levels: 1) predisposing factors or baseline characteristics of the individual patient, the disease, potential treatment and the prescribing physician, 2) factors influencing the relationship between the patient and prescribing physician, and patients’ interactions with the healthcare system during initial treatment decision-making and treatment maintenance, 3) patients’ beliefs and experiences regarding the treatment and incorporating the treatment into their daily lives, and 4) treatment outcomes and perceived benefits of adherence to therapy (Gater et al. 2012).

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<table>
<thead>
<tr>
<th><strong>Patient Characteristics</strong></th>
<th><strong>Disease Characteristics</strong></th>
<th><strong>Treatment Characteristics</strong></th>
<th><strong>Physician Characteristics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>High prescription burden</td>
<td>Dose</td>
<td>Number of active patients with CML in the past year</td>
</tr>
<tr>
<td>Gender</td>
<td>Temporary other illness</td>
<td>Treatment duration</td>
<td>Median duration of first visit with newly diagnosed CML patient</td>
</tr>
<tr>
<td>Quality of life / functional status</td>
<td>Concomitant disease</td>
<td>Treatment ADRs</td>
<td>Median duration of follow-up visits</td>
</tr>
<tr>
<td>Time from diagnosis to prescription fill</td>
<td>Risk of pregnancy</td>
<td>Financial cost to patient</td>
<td>Years of professional experience</td>
</tr>
<tr>
<td></td>
<td>Cancer complexity / complications</td>
<td>Second generation TKIs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Favourable physical properties (size, shape, color, taste)</td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 8. Conceptual model of adherence to oral TKI therapy in CML (modified from Gater et al 2012).** Note: ‘+’ denotes a direct influence relationship between a factor and reported levels of adherence (e.g. greater disease understanding is associated with greater levels of adherence) or reported levels of adherence and associated benefit (e.g. greater adherence associated with greater likelihood of achieving major/complete cytogenic response). Conversely, ‘−’ denotes the presence of an inverse relationship (e.g. lower QoL / functional status associated with higher levels of adherence).
5.6.2.1 Patient characteristics

Three patient characteristics have been found to impact on hematological cancer patients’ medication adherence: 1) forgetfulness, 2) patient education, knowledge and understanding, and 3) patients’ physical and emotional feelings (Hall et al. 2016). Forgetting to take the medication as prescribed was the most common reason for patient non-adherence (Eliasson et al. 2011).

CML patients’ education, knowledge and understanding influence medication adherence behavior. Patients with a secondary or higher level of education report higher levels of adherence than those with a lower level of education (Noens et al. 2009). Patients who reported inadequate medical knowledge (Wu et al. 2011) were more likely to be non-adherent. Patients who reported better knowledge of the impact of non-adherence on their disease and treatment were more likely to be adherent (Abraham et al. 2008, Noens et al. 2009). Patients who had a tendency to become complacent after long periods of disease control were less likely to adhere to their prescribed medications (Wu et al. 2011).

Patients’ physical and emotional feelings influence adherence. Higher levels of perceived QoL have been found to be associated with higher levels of medication non-adherence (Noens et al. 2009). On the other hand, higher levels of patient-perceived self-efficacy in relation to long-term medication behavior were found to be associated with better medication adherence (Noens et al. 2009). Reducing the impact that the drug had on the patient’s life was identified as a reason why patients did not adhere (Wu et al. 2011).

The findings are inconsistent if age is related to higher levels of adherence in CML patients. Some studies identify older age as being associated with non-adherence (Abraham et al. 2008, Noens et al. 2009), adherence as being associated with increasing age (Feng et al. 2006), or finding younger age to be related to non-adherence (Marin et al. 2010a; StCharles et al. 2009). Gender has not been consistently found to be associated with medication adherence rates. In two studies females reported higher rates of non-adherence (Darkow et al., 2007) or lower levels of adherence (Feng et al. 2006) and one study identified male gender as being related to higher rates of non-adherence (Noens et al. 2009).

5.6.2.2 Disease and treatment characteristics

Time since diagnosis was found to be associated with CML patients’ level of medication adherence in two publications (Noens et al. 2009, Abraham et al. 2008). Patients who were further from diagnosis had higher rates of medication non-adherence (Noens et al. 2009, Abraham et al. 2008). It is reported that adherence to oral TKIs decreases over time (Almeida et al. 2010).
Longer duration of treatment has been associated with higher levels of non-adherence (Noens et al. 2009, Abraham et al. 2008, Almeida et al. 2010).

Higher rates of treatment ADRs have been associated with higher rates of non-adherence (Marin et al. 2010a). Patients reduced, stopped or altered their medication without medical advice in an attempt to avoid treatment ADRs and to make them feel physically better (Eliasson et al. 2011, Jacobsen et al. 2011).

Participation in a clinical trial may increase adherence (Almeida et al. 2010, de Almeida et al. 2010). Taking medication independent of meals has been associated with higher rates of non-adherence (Marin et al. 2010a).

The physical characteristics of oral anticancer medications (e.g. size, shape, color, taste) and defining aspects of treatment regimens (e.g. dose and treatment duration) all influence adherence to TKIs for the treatment of CML (Gater et al. 2012). The role of medication type is still unclear. It has been associated with non-adherence (Almeida et al. 2010, Guérin et al. 2012, Oliveria et al. 2011, Wu et al. 2010b), with some studies reporting lower adherence in patients treated with dasatinib compared to those treated with nilotinib (Guérin et al. 2012, Wu et al. 2010b). Nilotinib use has been found to be related to higher rates of medication adherence compared to imatinib and dasatinib (Almeida et al. 2010). Another study found that patients treated with nilotinib reported poorer rates of adherence compared to dasatinib users (Oliveria et al. 2011).

There are different reports on the effect of dose on adherence in CML patients. In six studies (Noens et al. 2009, Marin et al. 2010a, Wu et al. 2010a, Darkow et al. 2007, StCharles et al. 2009) a higher dose or an increase in dose was found to be associated with higher levels of non-adherence. One study found a lower dosage of medication to be associated with medication adherence (Yood et al. 2012); while one study reported that a starting dosage of \( \leq 400 \) mg of imatinib was related to non-adherence (StCharles et al. 2009).

The data available on the effect of concomitant medications also vary. Adherence to TKIs has been found to decrease with an increase in the number of concomitant medications prescribed to patients (Feng et al. 2006, Noens et al. 2009, StCharles et al. 2009). On the other hand, one study found that a higher concomitant drug burden was related to higher rates of medication adherence (Efficace et al. 2012).

### 5.6.2.3 Patients’ social characteristics

Patients with CML living alone (Noens et al. 2009, Abraham et al. 2008) had higher levels of non-adherence, while higher levels of social support were
associated with higher adherence (Efficace et al. 2012). Low socioeconomic status has been associated with non-adherence (StCharles et al. 2009).

5.6.2.4 Healthcare system characteristics

The type of healthcare services accessed by patients with CML has been found to be associated with their level of medication adherence. Patients who made use of individual counseling about medication adherence or attended an institution with established protocols on managing patient adherence had higher adherence rates to their pharmacological treatment (Guilhot et al. 2010).

Some healthcare provider characteristics have been associated with patients’ level of adherence. A higher number of healthcare providers’ years of professional experience, higher number of active patients seen in the last year, median duration of first visit with a newly diagnosed patient, practising in a university or teaching hospital, and holding a specialization in hematology (Noens et al. 2009) have all been associated with higher medication adherence. On the other hand, shorter median duration of follow-up visits has been associated with increased non-adherence (Noens et al. 2009).

Physician and patient communication has been identified as affecting patients’ level of adherence (Eliasson et al. 2011, Wu et al. 2011). Miscommunication between patients and physicians (Wu et al. 2011), patients who were unable to access appropriate medical guidance (Wu et al. 2011) and patients who felt they were reassured by their physicians that their non-adherence would not have a detrimental effect on their treatment response (Eliasson et al. 2011, Wu et al. 2011) have reported higher levels of medication non-adherence.

5.7 Interventions to enhance medication adherence

Hematological cancers are increasingly being treated with self-administered medications, which may have long and complex treatment regimens (Agrawal et al. 2010). Strategies to improve medication adherence for patients with hematological cancers is critical given the evidence that there is a negative association between medication non-adherence and lower perceived disease severity (DiMatteo et al. 2007). Medication adherence has been found to decrease with long-term medication use (Gater et al. 2012), which may be problematic for many hematological cancers that require long-term treatment.

Adherence is affected by both behavioral and system barriers (Touchette and Shapiro 2008). Several intervention strategies, such as informational,
behavioral and combined strategies, have been explored to address adherence in chronic conditions. Informational interventions have been described as “cognitive strategies designed to educate and motivate patients by instructional means” (Touchette and Shapiro 2008). Behavioral interventions are designed to influence behavior through shaping, reminding, or rewarding desired behaviors (Kripalani et al. 2007). Combined interventions have features of both these (Touchette & Shapiro 2008). It has also been found that complex programs utilizing multiple interventions delivered over a longer period of time are more likely to achieve better outcomes (Peterson et al. 1984, Bailey et al. 1990, Piette et al. 2000, Farber and Oliveria 2004, Kripalani et al. 2007).

For most patients, non-adherence to pharmacotherapy is due to several factors present either at the same time or sequentially (D’Amato 2008, Doucette et al. 2012), and any single type of intervention is unlikely to be successful in improving adherence (Osterberg and Blaschke 2005, D’Amato 2008). Possible interventions range from simple to complex and can utilize the skills of a multidisciplinary team that includes pharmacists, nurses, physicians, and other healthcare professionals. Using multiple interventions and different methods over time may be the most successful approach (Touchette and Shapiro 2008).

Few published studies have addressed adherence improvement techniques in patients with cancer. The methods described for the general population have therefore been extrapolated for this group of patients (McCue et al. 2014).

**5.7.1 Good and open communication**

The most important aspect of medication adherence is creating and maintaining a good relationship between the healthcare professional and the patient and family, in which open communication is encouraged (Boyle and Bubalo 2007, Hansen 2012). The healthcare professional should discuss with the patient and family the expected outcomes of the therapy and the potential ADRs while modifying the information for the individual patient (McCue et al. 2014). The message should be kept simple and complete enough to meet the patient’s needs. Some patients need to be reassured that oral cancer treatments are effective, but that results will not be seen immediately (D’Amato 2008). Patients should be informed about the need for good medication adherence and the possible consequences of poor adherence (Eliasson et al. 2011).
5.7.2 Patient education

Patients and their caregivers have significant educational needs at the start of oral anticancer treatments (D’Amato 2008). It is recommended that whenever possible, the patient’s family members, a friend, or a caregiver should be present to receive the education with the patient (Boyle and Bubalo 2007, D’Amato 2008). All information should be delivered in verbal and written form (D’Amato 2008). The physicians can deliver the education, but this is more commonly handled by nurses or pharmacists (Schneider et al. 2011).

Extensive oral chemotherapy education should contain the following information: drug and indication, dose, dosing schedule, start date, administration, what to do if doses are missed, possible food and drug interactions, treatment-related ADRs and their management, clinic contact information, and safe handling instructions for the medication (McCue et al. 2014). The importance of medication adherence should always be communicated, together with the potential consequences of non-adherence. Patients should be advised not to stop or change the medication dose without consulting with their hematology healthcare team (McCue et al. 2014).

Unfortunately, in many cases patients with cancer may not internalize much of the content in the initial teaching session (McCue et al. 2014). They may be overwhelmed, especially if they have received the diagnosis at the same visit. The information might need to be repeated either at a subsequent visit or over the phone (McCue et al. 2014).

Patient education initiatives, including a combination of face-to-face contact and interactive technologies or videos, have proved to be the most effective (Gysels et al. 2004). Verbal instructions should always be accompanied by written material (McCue et al. 2014). Written information should be appropriate in terms of healthcare literacy level amount. It is easy for healthcare professionals to forget how strange and complex medical jargon can be. Some patients might read the information well but have difficulty translating it into action (McCue et al. 2014).

If the medication is to be given more than once a day, patients should be asked to tell the healthcare professional what times of the day they will take it. If the medication is to be taken on an empty stomach, patients should state when they usually eat and when, in relation to mealtimes, they will take the medication. Planning these aspects in advance will help ensure patients’ medication adherence (McCue et al. 2014). In an era of readily available and easily accessible information, patients can easily become confused and anxious, effectively suffering from ‘information overload’ (Kim et al. 2007).
5.7.3 Simplifying the medication regimen

The medication regimen should be made as simple as possible in order to improve adherence (D’Amato 2008). The dosing schedule of anticancer treatment is often not modifiable because many medications are administered just once daily. The total complexity of the medication regimen depends on all the medications a person is taking, not just the cancer treatment. A complete medication history should be recorded at each evaluation. Every effort should be made to decrease the total number of medications, making sure that each is useful and appropriate in the context of cancer treatment. Creating a medication schedule that requires fewer administration times per day will improve adherence (McCue et al. 2014).

5.7.4 Reminder tools

Forgetting to take medication is the most common reason cited by patients for non-adherence, and a variety of reminder tools may be of assistance (Boyle and Bubalo 2007, Doucette et al. 2012). Patients should be taught to take their medications with other routines in their daily lives, such as meals or brushing their teeth (Boyle and Bubalo 2007, Eliasson et al. 2011) and storing the medication in a visible and frequently used place (Eliasson et al. 2011). Patients may find pill dispensers to be helpful in remembering to take their medications and to verify that the dose has been taken (Osterberg and Blascke 2005, Boyle and Bubalo 2007, D’Amato 2008, Schneider et al. 2011).

New technological adherence aids have been invented during recent years in order to improve patients’ adherence. There are alarms available on watches or smartphones, text or phone reminders, and electronic pill dispensers that announce when a dose is due (Boyle and Bubalo 2007, D’Amato 2008, Schneider et al. 2011). Many recent studies have shown positive results with text messages as sole adherence aid (Lester et al. 2010, Castano et al. 2012, Foreman et al. 2012, Wald et al. 2014, Khonsari et al. 2015).

Written medication schedules, diaries, and charts may help some patients to stay organized and adherent (D’Amato 2008, Touchette et al. 2008, Schneider et al. 2011). The most appropriate tool is the one the patient prefers and will use consistently (McCue et al. 2014).

5.7.5 Follow-up and managing ADRs

The key to improving medication adherence is to provide close follow-up contact and support (Osterberg and Blascke 2005, Boyle and Bubalo 2007,
D’Amato 2008, Schneider et al. 2011). Many patients will have further questions about their medication only after they have begun to take it. Patients may have ADRs that may adversely affect their adherence (see Chapter 3.5 and 5.6.2.2). Follow-up contact usually happens by phone between regularly scheduled provider visits for ease and convenience. The first contact with the patient should happen within 1–2 weeks of starting the medication, both to provide support and to address early concerns. Follow-up contacts may become less frequent as patients have been on their medication for a longer time and are tolerating it well (McCue et al. 2014).

Managing toxicity from oral chemotherapy agents is crucial to helping patients stay on their medication (D’Amato 2008). Early ADRs may discourage patients from continuing their treatment, and patients do not always call for assistance when they need it. Patients should be encouraged to report ADRs and their severity so that management measures can be taken (McCue et al. 2014).

At each follow-up, patients should be asked if they are adhering to their medication regimen (Ruddy et al. 2009). This may be as simple as asking them how many doses they have missed in the last 1–2 weeks and why it happened. The adherence rate might stay high because patients know that the healthcare team will ask if they are taking their medications (McCue et al. 2014).

For patients with difficult adherence issues, guided counseling could be beneficial to explore more fully the reasons for non-adherence (see Chapter 5.7.6) (McCue et al. 2014).

5.7.6 Guided counseling

Motivational interviewing or guided counseling helps to explore the patient’s own motivation and skills for change (Possidente et al. 2005). This method focuses on enabling patients to discover and strengthen their own motivation for change. These skills can be learned by any healthcare provider and can help patients focus on their own goals for themselves (McCue et al. 2014). Guided counseling requires the provider to listen nonjudgmentally to the patient, avoid prescribing ‘fixes’ for the problem, and to use open-ended questions. It also points out how the patient’s goals and actions might be incongruent. Motivational interviewing skills can help facilitate open communication with patients facing any illness and treatment (McCue et al. 2014).

5.7.7 Cochrane systematic review

The Cochrane systematic review assessed the effects of interventions intended to enhance patient adherence to prescribed medications for medical
conditions, on both medication adherence and clinical outcomes (Haynes et al. 2008). Nieuwlaat et al. (2014) updated searches of The Cochrane Library in 2013 with no language restriction.

This systematic review included randomized control trials (RCTs) of interventions to improve adherence with prescribed medications, measuring both medication adherence and clinical outcome, with at least 80% follow-up of each group studied and, for long-term treatments, at least six months follow-up for studies with positive findings at earlier time points. The update included 109 RCTs published since their previous update in January 2007 (Haynes et al. 2008) bringing the total number of RCTs to 182. Studies were heterogeneous for patients, medical problems, treatment regimens, adherence interventions, and adherence and clinical outcome measurements, and most had a high risk of bias.

Of all 182 RCTs, 17 had the lowest risk of bias for study design features and their primary clinical outcome, 11 from the present update and six from the previous update. The RCTs at lowest risk of bias generally involved complex interventions with multiple components, trying to overcome barriers to adherence by means of tailored ongoing support from allied health professionals such as pharmacists, who often delivered intense education, counseling (including motivational interviewing or cognitive behavioral therapy by professionals) or daily treatment support (or both), and sometimes additional support from family or peers. Only five of these RCTs reported improvements in both adherence and clinical outcomes, and no common intervention characteristics were apparent. Even the most effective interventions did not lead to large improvements in adherence or clinical outcomes (Nieuwlaat et al. 2014).

The authors concluded that the effects were inconsistent from study to study, and only a minority of lowest risk of bias RCTs improved both adherence and clinical outcomes. Current methods of improving medication adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized (Nieuwlaat et al. 2014). Research in this field needs advances, including improved design of feasible long-term interventions, objective adherence measures, and sufficient study power to detect improvements in patient-important clinical outcomes (Nieuwlaat et al. 2014).

5.7.8 Interventions to improve medication adherence of patients with CML

Even though high medication adherence is crucial for clinical response in TKI treatment, little evidence exists to show whether interventions influence the
adherence of patients with CML. Only one previous study providing such evidence has been published (Moon et al. 2012). This was a cross-sectional study of Korean patients with chronic CML prescribed imatinib. The patients were assigned either to a counseling program or to receive standard treatment. The counseling program consisted of phone consultations with a nurse and daily text message reminders to take the medication. The control group received written information from their medical team. ‘Overall compliance’ was defined as the product of ‘persistency’ (percent of the number of days of imatinib prescribed versus 1 year) and ‘dose compliance’ (milligrams of imatinib that were actually taken versus milligrams that should have been taken). The overall compliance to imatinib of those who participated in the counseling program was 93% after the 36-month follow-up period compared to 76% for the standard treatment patients (p<0.001) (Moon et al. 2012).
6 Summary of the key findings of the literature review (Chapters 2-5)

CML is a clonal disease of the hematopoietic stem cells in the bone marrow, which leads to a marked proliferation of granulocytes in the blood (Goldman and Melo 2003). In almost all patients (95%), CML is characterized by a specific chromosome translocation known as the Philadelphia chromosome (Nowell et al. 1960, Rowley JD et al. 1973, Sawyers 1999). Most patients are diagnosed in the chronic phase of CML, which is an early, indolent stage of the disease, when 40% of patients are asymptomatic or may experience only mild CML-related symptoms (Kantarjian et al. 1993). Introduction of the first TKI, imatinib, caused a dramatic change in the management of CML more than ten years ago (Stone 2004). The prognosis of the patients improved and treatment moved from hospitals to patients’ homes. There are approximately 550 CML patients in Finland in 2016. CML medication costs the Social Insurance Institution Kela 15 million euros a year (Kela 2016).

The response to TKI is the most important prognostic factor (Baccarani et al. 2013). Several ADRs related to TKI therapy in CML are common to all approved TKIs, including myelosuppression, rash, nausea, diarrhea, fatigue, and musculoskeletal pain/arthralgia/myalgia, albeit occurring at varying frequencies depending on the TKI. Nevertheless, TKIs also have different patterns of ADRs, and this should be considered when choosing among the available molecules (Pinilla-Ibarz et al. 2015).

Documenting QoL and the ADRs of CML treatments from the patients’ perspective is necessary to evaluate overall treatment effectiveness and the net clinical benefits of newer therapeutic strategies (Efficace et al. 2012). In the last few years several studies have proved the feasibility and safety of imatinib discontinuation in CML. Forty to 60% of patients who achieved a stable undetectable BCR-ABL transcript (UMD; [MR4 or MR4.5] and discontinued imatinib, experienced long-term TFR (Mahon et al. 2010, Ross et al. 2013, Rousselot et al. 2014).

Guilhot et al. (2013) showed that patients with CML progress through five distinct stages: crisis, hope, adaptation, new normalcy, and uncertainty, and the ability to cope with these stages is affected by the degree of knowledge about the disease, comfort level with the physician, and optimism about the success of treatment (Guilhot et al. 2013).

A patient’s ability to adhere to the requirements of their medication regime is central to the successful delivery of self-administered anticancer treatments. Adherence represents a range of behaviors from taking all medication as prescribed to an occasionally skipped dose and taking few or no doses at all (Osterberg and Blaschke 2005). Different tools have been used to evaluate and
assess patients’ adherence to medication, and there is no ‘gold standard’ measure of medication adherence.

According to some studies, CML patients’ level of adherence ranged from 76% (Feng et al. 2006) to 98% (Casamartina et al. 2010, Ibrahim et al. 2010, Marin et al. 2010a, Marin et al. 2010b, Koren-Michowitz et al. 2012). It has been documented in the literature that physicians are inaccurate estimators of adherence and are ‘no better than chance’ at judging which patients are adherent and which are not (Wagner et al. 2001, Zeller et al. 2008). Little is known in the literature about how the treating physicians estimate their CML patients’ adherence to TKI therapies.

The factors influencing CML patients’ adherence to TKIs are complex: patient characteristics, disease and treatment, the patient’s social characteristics, and healthcare system related matters.

Few published studies have addressed adherence improvement techniques in patients with cancer (McCue et al. 2014). Even though high adherence is crucial for clinical response in TKI treatment, little evidence exists to show whether interventions influence adherence of patients with CML. Only one previous study providing such evidence has been published (Moon et al. 2012).
7 Aims of the study

The overall objectives of this study were to explore adherence to TKIs of patients with CML in Finland from different angles: 1) the patient’s own perspective, 2) the physician’s perspective, 3) treatment-related ADRs and 4) QoL, and to create a model to improve patients’ adherence to TKIs.

The specific study aims are the following:

1) To evaluate adherence to TKI medication (imatinib, dasatinib, nilotinib) in adult CML patients who had been on TKI medication for at least the last six months before the assessment in Finland (I).

2) To compare the adherence reported by the CML patients with that assessed by their physicians (experienced vs. observed adherence) (I).

3) To evaluate ADRs experienced by CML patients during peroral TKI treatment and the correlation of ADR symptoms with medication adherence and perceived QoL (II, III).

4) To investigate low-adherent CML patients’ experiences of their patient journey and identify reasons for not taking their TKI medication as prescribed (I, III).

5) To evaluate the influence of a tailored patient education program combining nurse-conducted counseling and interactive information technologies (IT) on adherence of patients with CML using TKIs after a nine-month intervention period (IV).
8 Patients and methods

8.1 Study context and design

This study applied both qualitative and quantitative methods (Table 4).

Table 4. Methods used in the subsudies (I-IV).

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Data sources utilized</th>
<th>Analysis</th>
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</thead>
<tbody>
<tr>
<td>I, II, III, IV</td>
<td>86 personal, open-ended theme interviews in 2012-2014. For Study IV also a second interview after 9 month follow-up (n=68)</td>
<td>Interviews of patients with CML</td>
<td>Qualitative analysis: Abductive content analysis</td>
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<td>Quantitative analysis: demographic data collected at the beginning of the interview; Descriptive statistics: frequencies, percentages, means, and medians</td>
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<td></td>
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<td>II: Spearman’s rho test</td>
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<td></td>
<td>III: Pearson’s chi-square (gender, employment status: working/not working, and usually the same doctor), Fisher’s exact test (marital status: in relationship/not in relationship, number of TKI doses, and use of pill dispenser). Mann-Whitney U test (age, age at diagnosis, time from diagnosis, number of doctor’s visits during the last 12 months, number of comorbidities and number of other medications).</td>
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<td>IV: Fisher’s exact test (MMAS class, MMAS questions, gender, education, TKI medication, treatment line, knowledge of the disease and treatment at baseline) between the groups. The Mann-Whitney U test (age, duration of the disease, MMAS score, number of co-morbidities, number of other medications) between the groups. The Wilcoxon signed rank test to compare changes within the groups.</td>
</tr>
<tr>
<td>I, II, III, IV</td>
<td>Self-reported adherence questionnaire</td>
<td>Morisky 8-Item Scale (MMAS)</td>
<td>Quantitative analysis:</td>
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<td></td>
<td></td>
<td></td>
<td>II: Spearman’s rho test</td>
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<td></td>
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<td></td>
<td>IV: Fisher’s exact test (MMAS class, MMAS questions) between the groups. The Mann-Whitney U test (MMAS score) between the groups. The Wilcoxon signed rank test to compare changes within the groups.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Descriptive statistics,</td>
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<tr>
<td>II</td>
<td>Questionnaire</td>
<td>ADR and QoL questionnaire</td>
<td>Quantitative analysis:</td>
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<td></td>
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<td></td>
<td>II: Spearman’s rho test</td>
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<tr>
<td>I</td>
<td>Questionnaire</td>
<td>Physician’s assessment on adherence questionnaire</td>
<td>Quantitative analysis:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Descriptive statistics; frequencies, percentages, means, and medians</td>
</tr>
<tr>
<td>I, III, IV</td>
<td>Questionnaire</td>
<td>Knowledge of the disease and treatment questionnaire</td>
<td>Quantitative analysis:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Descriptive statistics; frequencies, percentages, means, and medians</td>
</tr>
</tbody>
</table>
Study IV was a randomized multicenter intervention study adhering to the CONSORT statement (Figure 9). Patients were randomized by the main investigator (MK) into either an intervention group with additional adherence support or a control group receiving standard treatment (Figure 10). There was a stratified randomization design based on sex and age.

8.2 Patients

The study period was from June 2012 to September 2013 (I, II, III) and from June 2012 to August 2014 (IV). All Finnish secondary and tertiary care hospitals (n=20) treating CML patients were invited to participate in the study. Eight of them agreed to participate (Helsinki University Central Hospital, Tampere University Hospital, Turku University Hospital, Oulu University Hospital, Satakunta Central Hospital, Mikkeli Central Hospital, South Carelia Central Hospital and Central Hospital of Länsi-Pohja). The patients were recruited for this study by physicians treating CML patients in these hospitals. All patients recruited gave their written informed consent. The study protocol was approved by the ethics committees of the hospitals concerned.

Study IV was powered to detect a 20% difference in adherence as estimated using a two-sample T-test. In order to give 80% power (5% two-sided significance) in adherence rates at nine months, predicated on 95% for the intervention group versus 75% for the control group, a sample size of 25 patients was required in each group (treatment vs. control, 50 patients in total).
8.3 Methods

8.3.1 Tools to evaluate adherence

8.3.1.1 Adherence as experienced by patients

Patient-reported adherence (experienced adherence) was evaluated in Studies I-IV using Morisky’s 8-Item Medication Adherence Scale (MMAS) (Morisky et al. 2008, Chapter 5.3.1.1, Appendix 1). As this was the first time MMAS has been used in a Finnish-speaking patient group, the instrument was translated into Finnish using a method that assures its face validity (Sartorius and Kuyken 1994). MMAS was first translated from English into Finnish. The Finnish version was then independently translated by another translator back into English. If significant differences were apparent, they were discussed until equivalence between both versions was achieved.

The 8 MMAS questions were asked verbally at the beginning of the personal interviews with the patients (see Chapter 8.3.2). In Study IV adherence was assessed at baseline and at nine months by the main investigator (MK).

Items 2, 3 and 6 in MMAS were considered in the analyses as intentional non-adherence (“People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your Chronic myelogenous leukemia medication(s)?”; “Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it?”; “When you feel like your Chronic myelogenous leukemia is under control, do you sometimes stop taking your medication(s)?”). Item 1 was considered in the analyses as unintentional non-adherence (“Do you sometimes forget to take your Chronic myelogenous leukemia medication(s)?”).

8.3.1.2 Observed adherence

For Study I, in addition to experienced adherence, the treating physicians were asked to give their subjective opinion on patients’ adherence (observed adherence). If the patient did not have a long-term doctor relationship, the questions were put to the physician who had treated the patient during his/her last appointment in the hospital. The physician’s opinion was rated to represent 1) ‘high adherence’ if the physician thought the patient was taking the medication as prescribed (selection of item 1), 2) ‘medium adherence’ if there might be some problems with medication-taking (selection of item 2), and 3) ‘low adherence’ if the doctor thought the patient had severe problems and was non-adherent (selection of item 3). Experienced adherence was compared with observed adherence using the three-level rating system (high-medium-low) described above.
8.3.2 Patient interviews

All the patients participated in the in-person interview with the main investigator (MK) (Studies I-IV). MMAS questions were asked at the beginning of the interview (Studies I-IV). A semi-structured interview method with pre-defined key topics and themes was used. The interviews were conducted using a flexible structure, which allowed conversational, two-way communication between interviewer and interviewee (Mason 2004). Interviews were audiotaped and transcribed verbatim by a professional transcriber.

The interview themes followed the idea of the patient’s journey with CML from the time before diagnosis to the study point. The themes covered patients’ own perceptions of the following phases of the patient journey: getting the CML diagnosis, information gathering, satisfaction with the treatment and healthcare system, medication adherence, behavioral aspects, knowledge of the disease and its treatment, patient-reported ADRs and sociodemographic factors (social network and support) (Study III).

Each patient’s demographic data were collected during the interview as follows: gender, age, marital status, education, occupation, employment status, time from CML diagnosis, time from diagnosis to the start of TKI treatment, TKI medication, dose, line, duration of usage, co-morbidities, other medications, medication review, dosing time, number of medical doctor (MD) visits during the last 12 months, MD visits during the first year after the start of TKI, nurse contacts in 12 months, nurse contacts during the first year after the start of TKI, phone contacts in the last 12 months, and days in hospital/hospitalization for any reasons after CML diagnosis.

The patient’s knowledge of the disease and TKI treatment was evaluated by asking five questions. Every correct answer scored one point, i.e., the total score ranged from 0 to 5 points.

At the time of the interview, the therapeutic response to TKI was assessed according to the patient's individual follow-up schedule.

8.3.2.1 Evaluation of patient-reported ADRs

Patient-reported ADRs were assessed during the interview using a structured questionnaire (Studies II and III). The questionnaire consisted of a list of 19 CML and TKI treatment-specific symptoms, and six items assessing the symptoms’ interference with the patient’s daily life (QoL). Patients were asked about the ADRs they experienced at the time of the study using a list of symptoms collected from the most common ADRs caused by TKIs in phase three studies. The interviewer followed the standardized symptom inventory questionnaire and every symptom was investigated by asking, “After the start of the TKI treatment have you suffered or are you currently suffering from the
(mentioned) symptom”. The following alternatives were given: 1) not applicable, 2) has suffered before, but not at the moment (these answers were not included in the analysis), or 3) yes, I am currently suffering from this symptom (included in the analysis). The number of patient-reported ADRs was taken as a ‘symptom score’, each reported symptom yielding one score (score range 0-1).

8.3.2.2 Evaluation of QoL

The patient interview also included six structured questions assessing functional impairment associated with TKI treatment (QoL) (Study II). QoL was assessed as a negative influence of patient-reported ADRs on six items: mood, general health, enjoyment of life, walking, relationships and work in general. Each item scored one point (i.e. the patient answered 'yes'), leading to a maximum score of six. This was considered as a measure of QoL. If the patient did not report any negative influence on his/her daily QoL, the score was ‘0’. The correlation between ‘QoL score’ and ‘symptom score’ was measured.

8.3.2.3 Follow-up interview in Study IV

In Study IV the patients were interviewed nine months after starting the intervention. The intervention group patients were also asked to give their opinion of the educational material, adherence aids and face-to-face counseling by using a structured questionnaire at the end of the interview.

8.3.3 Intervention

The intervention in Study IV was based on tailored patient education combining nurse-conducted face-to-face counseling and interactive information technologies. The education was provided by hematology nurses trained to deliver the intervention. The nurses’ knowledge of CML and adherence to medication was assessed. All were trained in adherence and patient counseling to be able to support patients with the adherence aids and material used in this study (Table 5). The main training session lasted one hour. There were also additional rehearsals before the first patient counseling session.

Each patient in the intervention group attended a one-on-one tailored education session with a hematology nurse. The session repeated the same content in three different ways: audiovisual, verbal and written. At the beginning of the session, each patient watched a 5-minute video via an iPad at
Table 5. Adherence aids used, their mode of delivery, key contents and purposes.

<table>
<thead>
<tr>
<th>Adherence aid</th>
<th>Mode of delivery</th>
<th>Key content</th>
<th>Purpose</th>
<th>Special features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Video (5 minutes)</td>
<td>Audiovisual, can be repeated by the patient at home</td>
<td>Knowledge of the disease, explaining the reasons for the importance of medication taking</td>
<td>To increase understanding of the disease, treatment goals, importance of medication taking and psychosocial factors in an audiovisual story form</td>
<td>Video entitled “Treat yourself correctly” - Story told by a doctor and a patient</td>
</tr>
<tr>
<td>Patient counseling (30 minutes)</td>
<td>Verbal, interactive</td>
<td>Knowledge of the disease, goals for treatment, understanding lab tests, importance of medication taking, side effect management, psychosocial support</td>
<td>See above, encourage the patient in self-management in an interactive setting</td>
<td></td>
</tr>
<tr>
<td>Information booklet</td>
<td>Visual, repeatable at home</td>
<td>Knowledge of the disease, goals for treatment, importance of medication taking, side effect management, psychosocial support</td>
<td>Increase understanding of the disease, treatment goals, importance of medication taking and psychosocial factors in written form including figures/pictures</td>
<td>Ability to keep a symptom and medication diary. 15 pages long with an appendix including a medication card and a side effect diary.</td>
</tr>
<tr>
<td>Website</td>
<td>Visual, IT, repeatable</td>
<td>Reminder of medication taking time</td>
<td>To remind patients to take the medication on time</td>
<td>Ability to manage features from the website</td>
</tr>
<tr>
<td>Text messaging</td>
<td>IT, repeatable</td>
<td>Reminder of medication taking time</td>
<td>Ability to manage features from the website</td>
<td></td>
</tr>
</tbody>
</table>

The nurse recorded any questions asked by the patient after he/she had watched the video. This was followed by a 30-minute face-to-face counseling session based on the booklet and website information.

The content of the educational video, patient booklet and internet website was based on the following learning objectives: CML as a disease, goals for TKI treatment, the importance of taking TKI medication as prescribed, and self-management of adverse drug reactions. Patients were also taught how to use different adherence aids to remember to take their medication on time. They were also told about the psychosocial factors related to CML and the importance of social networking. Patients were asked to keep a diary on any adverse drug reactions and to score the severity of their symptom(s). Patients were also asked to keep a record of all new medication prescribed to them.
during the follow-up period. All the educational material was placed on a limited-access website (www.kmlhoito.fi). Patients received their own username and password to access the site. The number of patient visits to the website was recorded daily.

Patients were offered daily text messages to their mobile phones based on the dosing regimen of their treatment to help them remember the time to take their medication. They were also able to manage the text message settings from the website, e.g. change the timing of the message or, if they wished, stop receiving the messages altogether.

8.4 Data analysis

8.4.1 Qualitative analysis
In Study III the following step by step analyses were used: 1) quantitative comparison of patients with high and low adherence; 2) qualitative analysis of reasons for poor adherence in the group of patients that scored low in Morisky’s test; 3) model development of the CML patient journey based on the qualitative narratives and the previous model (Guilhot et al. 2013).

The interview recordings were transcribed and analyzed using thematic analysis with abductive approach (Kylmä and Juvakka 2007). The purpose of the thematic analysis is to identify the important patterns and themes across the data that provide answers to the research question (Hämeen-Anttila and Katajavuori 2008). The themes used in the semi-structured interviews provided a framework for the analysis. The first step was to become familiar with the data. The important and interesting features of the data were then identified and labeled as codes. The codes were categorized into potential subcategories, themes, so that all relevant data were included. Finally, the themes were abstracted into broader categories that were named accordingly. Transcripts were coded independently by another researcher to ensure reliability. Codes and themes were then compared and discussed between two researchers (MK, VY) to make sure they were consistent.

‘Patient journey’ was defined in the interview questions as the time before CML diagnosis, diagnosis, life after diagnosis and current situation. The different stages of the journey were analyzed from the patients’ stories and added to the patient journey model (Figure 11).

8.4.2 Statistical analysis
In Study I the statistical analysis of the data was based on descriptive statistics calculated as frequencies, percentages, means, and medians. The kappa coefficient was calculated between the patient’s and the doctor’s assessment of adherence.
In Study II each patient’s MMAS score was compared with the quality of life score and symptom score. The statistical analysis was performed using IBM SPSS Statistics for MAC version 21.0 (IBM Corp, Armonk, NY, USA). Spearman’s rho test was used to test the difference between adherence, QoL and ADRs. For statistical analysis an α-value of 0.05 was considered statistically significant.

In Study III the statistical analysis was performed using IBM SPSS Statistics, version 21.0. The quantitative variables were presented with mean, SD, median and percentages. Non-parametric statistical tests were used because the data were not normally distributed. Tests used for categorical data were Pearson’s chi-square (gender, employment status: working/not working, and usually the same doctor), and Fisher’s exact test (marital status: in a relationship/not in a relationship, number of TKI doses, and use of pill dispenser). The Mann Whitney U test was used for continuous parameters (age, age at diagnosis, time from diagnosis, number of doctor’s visits during the last 12 months, number of comorbidities and number of other medications).

In Study IV the statistical analysis was performed using IBM SPSS Statistics for MAC version 21.0 (IBM Corp, Armonk, NY, USA). The baseline characteristics of the control and intervention groups were compared. Fisher’s exact test was used to compare non-continuous variables (MMAS class, MMAS questions, gender, education, TKI medication, treatment line, knowledge of the disease and treatment at baseline) between the groups. The Mann-Whitney U test was used to compare continuous variables (age, duration of the disease, MMAS score, number of co-morbidities, number of other medications) between the groups. These tests were not used to compare changes from baseline to follow-up. For this purpose we used the Wilcoxon signed rank test to compare changes within the groups. For statistical analysis an α-value of 0.05 was considered statistically significant. Descriptive statistics included calculating frequencies, percentages, means and medians.
9 Results

This chapter summarizes the key findings of the original studies (I-IV).

9.1 Patient population

9.1.1 Patient population (Studies I-III)

During the 15-month study period (from June 2012 to September 2013), 120 patients were contacted in eight hospitals (four tertiary and four secondary care hospitals) (Studies I-III). A total of 86 patients participated in the study (approximately 20% of all Finnish CML patients). Twenty-seven patients declined and seven dropped out after the initial agreement because of a deterioration in their general health or because they had second thoughts. In this patient population the mean time from CML diagnosis was five years (median four years, range 1-17 years). The mean age at diagnosis was 53 years (median 52 years, range 19-79 years). Patient characteristics are shown in Table 6.

9.1.2 Patient population (Study IV)

Of the 86 patients enrolled, 43 were randomized into the intervention group and 43 into the control group before the baseline interview (IV). The groups were age and sex matched. A total of 68 patients completed the study (79% of the original study group): 35 in the intervention group (84%) and 33 in the control group (77%). Eighteen patients dropped out from the study during the nine-month follow-up. Of these, eight patients discontinued their TKI medication as they had been in optimal molecular response for more than two years (six in the intervention group and two in the control group). One patient from the intervention group was transferred to stem cell transplantation due to progression of the disease. Nine patients were lost or could not be contacted after the follow-up.

In this patient population the mean time from CML diagnosis was 4.8 years (median four years, range 0.5–17 years). Most of the patients (81%) were receiving imatinib, 9% dasatinib and 10% nilotinib. Of the patients, 54% were on first-line and 28% on second-line treatment. The patients had an average of 1.8 co-morbidities, the most common being high blood pressure and hypercholesterolemia in both groups. There was no difference between the intervention and control groups.
<table>
<thead>
<tr>
<th>Variables</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td>Male</td>
<td>45 (52.3)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>41 (47.7)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean</td>
<td>57.8 (12.1)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>25-83</td>
</tr>
<tr>
<td><strong>Age at diagnosis (years)</strong></td>
<td>Mean</td>
<td>52.7 (12.3)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>19-79</td>
</tr>
<tr>
<td><strong>Time from diagnosis (years)</strong></td>
<td>Mean</td>
<td>51 (3.7)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.5-17</td>
</tr>
<tr>
<td><strong>Co-morbidities and medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of other diseases</strong></td>
<td>Mean</td>
<td>1.6 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-8</td>
</tr>
<tr>
<td><strong>Number of other cancers</strong></td>
<td>Mean</td>
<td>0.1 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-3</td>
</tr>
<tr>
<td><strong>Number of other prescription medicines</strong></td>
<td>Mean</td>
<td>2.1 (0.4)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-10</td>
</tr>
<tr>
<td><strong>TKI medication related factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TKI medication, n (%)</strong></td>
<td>Imatinib</td>
<td>68 (79.1)</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>9 (10.5)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td>9 (10.5)</td>
</tr>
<tr>
<td><strong>Line, n (%)</strong></td>
<td>First</td>
<td>47 (54.7)</td>
</tr>
<tr>
<td></td>
<td>Second</td>
<td>25 (29.1)</td>
</tr>
<tr>
<td></td>
<td>Third</td>
<td>13 (15.1)</td>
</tr>
<tr>
<td></td>
<td>Fourth</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td><strong>Number of TKI doses per day, n (%)</strong></td>
<td>One</td>
<td>72 (83.7)</td>
</tr>
<tr>
<td></td>
<td>Two</td>
<td>14 (16.3)</td>
</tr>
<tr>
<td><strong>TKI medication taking time, n (%)</strong></td>
<td>Morning</td>
<td>27 (31.4)</td>
</tr>
<tr>
<td></td>
<td>Lunch time</td>
<td>23 (26.7)</td>
</tr>
<tr>
<td></td>
<td>Evening</td>
<td>21 (24.4)</td>
</tr>
<tr>
<td></td>
<td>Morning+evening</td>
<td>14 (16.3)</td>
</tr>
<tr>
<td></td>
<td>lunch+evening</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td><strong>Visits and contacts with healthcare personnel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MD visits in the last 12 months</strong></td>
<td>Mean</td>
<td>2.2 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-12</td>
</tr>
<tr>
<td><strong>MD visits during first year</strong></td>
<td>Mean</td>
<td>4.07 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1-12</td>
</tr>
<tr>
<td><strong>Phone contacts in the last 12 months</strong></td>
<td>Mean</td>
<td>0.7 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-12</td>
</tr>
<tr>
<td><strong>Adherence aids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Written treatment plan, n (%)</strong></td>
<td>No</td>
<td>86 (100)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td><strong>List of medications, n (%)</strong></td>
<td>No</td>
<td>82 (95.3)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td><strong>Doset, n (%)</strong></td>
<td>No</td>
<td>69 (80.2)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>17 (19.8)</td>
</tr>
<tr>
<td><strong>Mobile phone reminder, n (%)</strong></td>
<td>No</td>
<td>76 (88.4)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>10 (11.6)</td>
</tr>
<tr>
<td><strong>Knowledge total score, n (%)</strong></td>
<td>0</td>
<td>28 (32.6)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>30 (34.9)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>15 (17.4)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7 (8.1)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2 (2.3)</td>
</tr>
</tbody>
</table>

SD= standard deviation. *At the time of adherence evaluation.
9.2 Medication/treatment

Most of the patients (79%) were receiving imatinib, 11% dasatinib and 11% nilotinib and on first (55%) or second (29%) line treatment (Studies I-III). First-line treatment means that the patients were on the same active substance and dose as when they had started the treatment. Most (84%) of the patients were taking a single dose, usually in the morning (31%) or during lunchtime (27%). None of the patients had a written treatment plan and only 5% (n=4) had a list of their medications.

Seventy-six percent of the patients had other diseases (mean 2, median 1, range 0-8). Eight percent of the patients had previously had a diagnosis of at least one other cancer (range 0-3). Due to these comorbidities the patients were also using other medications, the mean number of which was 2 (median 1, range 0-10).

Among patients who completed Study IV, most (81%) were receiving imatinib, 9% dasatinib and 10% nilotinib. Of the patients, 54% were on first-line and 28% on second-line treatment. The patients had an average of 1.8 co-morbidities, the most common being high blood pressure and hypercholesterolemia in both groups. There was no difference between the intervention and control groups.

9.3 Response to TKI treatment

The response to TKI treatment was high (Study I), with 81% of the patients showing an optimal response according to European LeukemiaNet 2013 recommendations (Baccarani et al. 2013). One-third of the patients had shown a major molecular response (MMR, MR3.0). The proportion of patients with MR5.0 was very high (23%).

9.4 Knowledge of the disease

The CML patients’ knowledge of the disease and its treatment was poor as they scored on average 1 point out of the maximum 5 (Study I). One-third of the patients scored nothing from the questions, which means they did not understand their disease, how the medication works or the consequences of not taking the medicine as prescribed. Only 2% (n=2) of the patients scored the maximum 5 points.
9.5 Physician-related characteristics

Thirteen physicians were involved in Study I. Twelve of them were specialists in hematology and one in internal medicine. The patients had had on average two MD visits during the last 12 months (median 2, range 0-12). There was no difference in the number of MD visits between different MMAS groups. Two-thirds of the patients had a long-term relationship with their physician (67%), while the other 33% reported their physician changed every second visit.

9.6 Experienced and observed adherence

Despite the high molecular response rates to TKI treatment, adherence according to MMAS was not good in most of the patients: less than a quarter (23%) of the patients showed high adherence, 56% medium adherence, and 21% low adherence (Study I). Unintentional non-adherence was common, particularly forgetting to take the medication (48% of patients). One-fifth of the patients had sometimes forgotten to bring along their medication when leaving home or travelling. Patients in the present study had a low level of intentional non-adherence behavior. Stopping taking the medication when feeling worse after drug administration without telling the doctor was rare: only 11% had done so. Twenty-two percent of the patients reported taking their medication every day to be a real inconvenience (I, III).

No significant statistical association/correlation was found between non-adherent and adherent patients regarding gender, age, time from diagnosis, ADRs, knowledge, education, number of comorbidities or number of other medications. The patients with low adherence had fewer comorbidities (p=0.009) and concomitant medications (p=0.002) than highly adherent patients (III).

There was a considerable difference between observed and experienced adherence: 94% of the patients were highly adherent according to the physicians’ assessment (I). The Kappa coefficient between patient’s and physician’s assessment of adherence was extremely low (-0.004), indicating that there was no agreement between the two assessments. Adherence was assessed by the physicians as medium in 5% of patients and low in only 1%. Compared to patient-reported adherence, the physician’s assessment was too optimistic in 73% of cases, realistic in 25% and pessimistic in 2%. In seventeen cases (20% of the total patient population) the physician had assessed the patient as highly adherent, whereas the MMAS scored patient adherence as low. In 45 cases (52% of the patients), patients whose adherence was medium according to MMAS were assessed by the physician as highly adherent (I).
9.7 Patient-reported ADRs and their influence on medication adherence

The incidence of patient-reported ADRs was high (II). At the time of the study 97% of the patients reported suffering from at least one ADR, which had started after the start of TKI treatment. The most commonly experienced ADRs were muscle soreness or cramp (69/86, 80%), swelling of hands, legs, feet, or around the eyes (59/86, 69%) and fatigue (43/86, 50%). The patient-reported severity of ADRs was mainly mild to moderate. Thirteen patients reported their ADRs as severe. These symptoms were cramp (n=3), swelling (n=5), rash (n=3), diarrhea (n=1) and disturbed sleep (n=1). There were also differences in ADR profiles between the three different therapies (II). No correlation was found between adherence and patient-reported ADRs, because symptoms were equally common in each MMAS adherence class (high, medium and low).

9.8 Influence of ADRs on patients’ QoL

More than half of the patients felt the ADRs had a negative influence on their daily QoL (II). A quarter of the patients reported the symptoms had a negative influence either on their mood, general condition or enjoyment of life. Patients who felt their symptoms negatively affected their QoL suffered from an average of eight different symptoms (range 3-15, median 8).

Compared with the total study population, the incidence of all symptoms other than nausea and vomiting was higher among patients who said their symptoms negatively affected their daily life than among those who reported no such influence (II). More men reported their symptoms to have a negative influence on their daily life than women (53% vs. 44%). More than half of the imatinib users (54%), one-third of the dasatinib users (33%) and one-fifth of the nilotinib users (22%) experienced symptoms which had an unwanted influence on their daily life.

9.9 Reasons for non-adherence – qualitative analysis

9.9.1 Intentional and unintentional non-adherence

Both intentional and unintentional non-adherence to prescribed TKIs was reported, of which unintentional non-adherence was more frequent among the study patients. In a few cases patients reported intentional non-adherence as a
consequence of some unintentional reason. The most common reason for unintentional non-adherence was forgetting to take the medication (I, III). Based on the interviews, patients’ unintentional reasons for not taking the medicine were forgetting, not having the medication with them, falling asleep early, and skipping a dose due to other illnesses (e.g. stomach upsets). Intentional reasons for not taking the medication as prescribed were ADRs, holidays, social events, changed dose and inability to schedule the medication regimen with fasting (III). Women felt inconvenienced by their treatment plan more often than men. They also missed taking their medication due to reasons other than forgetting more often than male patients.

“Now and then, if my morning is a bit out of the ordinary. Usually I take it in the morning, so if I’m somehow in a hurry or leave home at an unusual time, I might be in the car before I realise that, heck, I’ve forgotten it.”

“And then I sometimes remember (the medicine) in the evening when I’ve already gone to bed, and if I haven’t eaten anything in the evening, I won’t go back upstairs to eat, I definitely don’t take them if I haven’t eaten. I’ve done it a few times, and then I get a nasty headache and don’t feel well, and it takes another hour before I feel better, so I just leave it; my husband doesn’t like it but I don’t always tell him.”

A weekly pill dispenser used as a memory aid did not provide help for some of the patients using it; patients reported that they either forgot to fill it or that they still would forget to take the medication. Sometimes patients faced challenges in medication-taking that was beyond their control (e.g. stomach upsets).

9.9.2 ADRs

The high incidence of ADRs is described in Chapter 9.7. Patient interviews indicate that ADRs were the most commonly reported barriers to adherence. Several patients also reported skipping or reducing the dose due to ADRs.

“In the morning after medication taking I felt awful. I was not able to do anything. I reduced the dose – and felt better”.
9.9.3 Self-regulation

In the interviews, self-regulation of medication taking during holiday and traveling was often mentioned as the reason for deciding not to take the medication (III). Patients explained they did not want to think about their disease and routines around it or to deal with ADRs while traveling. Socializing was another reason for skipping the dose or changing the taking time to avoid ADRs. Some patients reported sometimes remembering their daily medication too late, for example when they were already in bed or if the taking time was timing to take the medication with food or in a fasting state was challenging and contributed to skipping the dose.

“Usually, if we are going to a party or have a day off, for example, I will take the medicine already in the morning or skip it. You never know, if you are going to get headache or nausea or something else.. It’s not nice, when you are not feeling well. I understand I should take the medicine, but if there is that kind of situation, I will not take them”.

9.9.4 Contributing healthcare system factors

All CML patients in the study were lacking the therapy plan and only a few had the medication list (I, III). It was found in the knowledge test (I, III) that patients did not fully understand the disease and its treatment. On the other hand, understanding the consequences of not taking the medication and the goal of the treatment were regarded as motivating factors by the patients with low adherence to adhere to their medication (III).

“Of course it’s motivating if you have a goal. I like it that for instance experienced doctors tend to sort of give you a goal to aim for or say that we’re trying to reach a value that’s lower than that... Of course it’s been helpful to know that they’re keeping an eye on how this is going.”

9.10 Impact of the educational intervention on adherence

At the baseline the groups were similar in adherence as assessed by MMAS class (Fisher’s exact test p>0.05). No change in adherence was observed in half of the patients, while in 27% adherence decreased over time. The change from baseline to follow-up in the control group was statistically non-significant
(Wilcoxon signed rank test, p=0.593). In the intervention group adherence remained the same in half of the patients, but improved in 49% (Wilcoxon signed rank test, p<0.0001).

Eight patients in the intervention group and seven in the control group were already highly adherent and had a maximum MMAS score (8) at baseline. The MMAS score of six (86%) of these patients declined during the follow-up in the control group, compared with only one patient (13%) in the intervention group.

In the intervention group the MMAS score increased more often (21/35) than in the control group (11/33) (60% vs. 33%, respectively, Mann-Whitney U test, p= 0.001). The MMAS score declined in almost half (49%) of the patients in the control group, but in only 9% of those in the intervention group (Mann-Whitney U test, p=0.001).

9.10.1 Patient experiences on the intervention

The point that the patients remembered most often from the intervention in the follow-up interview was, “One has to take the medication as prescribed, on time” (14/35). A majority of the patients (30/35) found the education useful, the most useful parts being face-to-face counseling (30/35), the educational booklet (29/35) and the video (25/35). On average 23 patients visited the website per month. Seven patients had forgotten the content of the education, explaining that this was mainly due to their advanced age and memory impairment.

One-third (n=11) of the patients chose to receive the tailored daily text message reminder. Only three of them (27%) perceived the text message as useful. One-third thought the text message interrupted their daily routines. The reason reported for not wanting the text message reminder was “no need” in all cases.

9.11 Patient experiences on the patient journey

The main findings of the patient journey are described in Figure 11.
Most patients were asymptomatic when diagnosed with CML. In many cases the disease was unexpectedly diagnosed after a routine physician visit. The majority of the patients (94%) experienced the diagnosis as “shock, crisis or the end of the world”. One-third of the patients were told of the diagnosis on the phone. Patients would have preferred to hear ‘the bad news’ face to face from their doctor.
The information patients received about CML from the doctor at the time of diagnosis varied amongst the patients: 38% (7/18) felt they received adequate information about CML and its treatment, almost two-thirds (11/18) did not think they got enough information, and one patient had received incorrect information.

The patients said it was important to receive information that was supportive and encouraging, highlighting the facts that CML is a well-studied, chronic, treatable disease with effective medication and can be managed at home. It was important to use non-technical language. Patients preferred the doctor’s way of avoiding the word ‘cancer’ and referring to a serious but treatable chronic condition instead. One patient even felt that the doctor had been understating the seriousness of CML by saying it is not as bad as it sounds. A few patients felt they received too much information to handle too soon. In most cases the provision of adequate information relieved the patients’ fear of death and the severity of the situation. Some of the patients had negative experiences regarding the way the information was given. A few felt that the doctor did not have sufficient knowledge of the disease (III).

To learn more about CML and to understand the disease better, patients had searched for information from different sources. Ten of the patients had actively sought more information about the disease. The internet was the most commonly used tool, half of the patients having used it to find out more about CML itself, the treatment and other CML patients’ experiences of the disease. Other information sources used were brochures provided by the hospital or mailed home, and library books. Understanding more about the nature of CML was important for the patients and made them feel more comfortable about dealing with the disease. However, two patients said they did not want to learn more about CML or needed more time to be ready to receive information.

The patients were not aware of what caused the disease and what was happening in their body or how the medication works (I, III). Few of the patients understood the consequences of not taking the medication. This was seen as a factor motivating them to adhere to the treatment. The knowledge scores of patients who had reported they had searched for information by themselves were better than those of patients who did not seek more information.

9.11.2 Healthcare system

The majority of patients with poor adherence said they were very pleased with their healthcare personnel and the treatment received in general (III). Interactions with doctors and nurses were important during the diagnosis and follow-up appointments. Two-thirds of the patients usually saw the same doctor. Both informational and emotional support from the doctors and other
healthcare personnels had a positive influence on the patients. Especially at the beginning, when there were lots of concerns and questions about the newly diagnosed CML, the doctor’s support was considered important. Support consisted of discussing with the doctor about the disease, its prognosis, the treatment and its goals, and ADRs in an encouraging way. It was also important that the doctor was knowledgeable and had time to talk in person. For the patient it was reassuring to know that if there were any concerns they would always get addressed.

A lack of interaction and information from the healthcare personnel had a negative impact on patients. Frequently changing doctors meant there was no continuous support. Six patients said they were not informed about the available services such as psychologists, social workers or other support provided by the hospitals. Services were not always easily available. Laboratory results were often sent to patients by mail. In many cases patients said they did not understand the results.

Patients who felt they did not receive any mental support from the hospital still thought that their care was good and taken seriously. The care provided by the hospitals was considered excellent by all the patients. One stated, “You feel you are in good hands there”.

9.11.3 Future intentions

Even though only 44% of the low-adherent patients in the study experienced the TKI treatment as inconvenient, most of the patients (94%) said they were willing to stop taking the medication in the future if possible (see Chapter 3.7, III).

9.11.4 Key findings of the study

The key findings of the study are presented in Figure 12.
**Adherence**
Adherence was low (I)
Physician’s assessment too high (I)
Forgetting most common reason for non-adherence (I, III, IV)
Self-regulation (III)
Good treatment responses despite of poor adherence (I)

**Experiences on patient journey (III)**
Diagnosis experienced as crisis or end of life
Information at the time of diagnosis insufficient
In general satisfied with healthcare
Need to understand the goal of treatment

**Patient**
Knowledge of disease and its treatment poor (I)
Willing to take medication (I-II)

**ADRs & QoL (II)**
High prevalence despite of adherence level
Affect to QoL

**Intervention (IV)**
Intervention improved adherence
Without intervention adherence behaviour tended to decline
Especially intentional non-adherence improved in intervention group
Patients preferred face-to face counseling

**Partnership/Support (I, III, IV)**
Lack of written treatment plans
Lack of medication lists
Lack of psychological support (III)

**Figure 12. Key findings of the study.**
10 Discussion

This thesis investigated the patient journey and medication adherence of patients with CML undergoing treatment with TKIs in Finland. This work consisted of two parts: a literature review and an empirical part.

In the literature review, evidence on the non-adherence of CML patients to TKIs was examined (see Chapters 2, 3 and 4). The first studies on the QoL associated with TKI treatments (Chapter 3) have been published during the last years and new assessment tools have been developed. The level of adherence of CML patients and the reasons for patients’ non-adherence have also been widely studied in recent years (see Chapter 5). Unfortunately, publications on interventions to improve the medication adherence of CML patients to TKIs are lacking. In view of this, the literature review discussed interventions to improve medication adherence in general (see Chapter 5).

The empirical part (later study) of this thesis focused on the patient journey of CML patients in Finland: patients’ experience on their journey with CML, adherence to TKIs, patient-reported ADRs, and QoL (Studies I-IV). These perspectives were chosen because they are relevant for understanding the background and consequences of adherence. Currently, the literature provides no information on these aspects of care in Finland and even the evidence from other countries is limited. Finally, the influence of tailored patient education on adherence to TKI medication among patients with CML was investigated through a controlled intervention study (Study IV).

The study employed a novel approach to adherence assessment by CML patients and their physicians. We found the same, quite low patient-reported adherence to TKI treatments that has been found in most previous studies (Noens et al. 2009, Marin et al. 2010b, Ibrahim et al. 2011). From the physician’s perspective this study provides new information on the discrepancy between patient-experienced and physician-observed adherence. In most of cases with low patient-experienced adherence, physicians estimated adherence to be high.

This study provides new information from the patient’s perspective on the prevalence of patient-reported ADRs during TKI treatment (II). This prevalence was high and much higher than in clinical trials, which in most cases study the efficacy and safety of treatments. Even though the ADRs did not influence adherence, they had a significant influence on patients’ QoL. The findings also provide new information about patients’ experiences on their journey with CML (III).

A lack of interaction and information from healthcare professionals had a negative impact on non-adherent study patients (III). Frequently changing doctors meant there was no continuous support. Laboratory results were often
sent to patients by mail. In many cases patients reported they did not understand the results. Nevertheless, the overall care provided by hospitals was considered excellent by all patients.

The ability to cope with different stages on the patient journey has been found to be affected by the degree of knowledge about the disease and comfort level with the physician (Guilhot et al. 2013). The present study provides new information on patients’ knowledge of the disease and its treatment, which was poor irrespective of adherence level (I, III). Few patients understood the consequences of not taking the medication. Understanding the treatment goals was seen as a motivating factor to adhere to the treatment. A real partnership between healthcare professionals and patients would improve patients’ abilities to follow their treatment plans.

It appears that this is the first study assessing the impact of tailored patient education on the medication adherence of patients with chronic phase CML. Tailored patient education improved the adherence of patients with CML after a 9-month follow-up (IV). Without the additional support, adherence behavior tended to decline. Most of the patients with CML involved in the study found enhanced patient education and adherence support useful. This study also provides new information on patients’ preferences regarding education and adherence aids. Most valued was face-to-face counseling by a hematology nurse. The information booklet focusing on the basic facts about CML and its treatment with TKIs was perceived almost as useful as face-to-face counseling. Clearly least valued were text message reminders. This indicates that patients with CML need personal contact and communication with their healthcare providers. They also need easy access to written information tailored for their specific needs.

10.1 Key findings in relation to earlier studies

10.1.1 Adherence

We found the same, quite low patient-reported adherence to TKI treatments that has been found in most previous studies (Casamartina et al. 2010, Ibrahim et al. 2011, Marin et al. 2010a, Marin et al. 2010b, Koren-Michowitz et al. 2012).

According to our findings, physicians seem to be too optimistic in assessing their patients’ adherence (I). Previous studies with other patient groups and medications show that physicians are inaccurate in assessing adherence and judging which patients are adherent and which are not (Wagner 2001, Osterberg and Blaschke 2005, Zeller et al. 2008, Noens et al. 2009). When estimating the degree of adherence for any particular patient group, physicians have been shown to be accurate only 10–40% of the time, for both medication
and other treatments (Turner and Hecht 2001, Parker et al. 2007, Morton et al. 2008). In the Belgian ADAGIO study physicians believed that on average 93% of CML patients on imatinib were adherent during the first month after diagnosis and that 87% were adherent after one year of treatment (Noens et al. 2009).

One reason for this discrepancy in adherence estimates by patients and their physicians may be clinical treatment outcomes. Despite the low patient-reported adherence rate assessed by MMAS, most of the patients (81%) had an optimal molecular response to their treatment according to ELN 2013 Guidelines (Baccarani et al. 2013). Consequently, we assume that good clinical treatment outcomes were the reason why the physicians gave a higher estimate of adherence than the patients. On this basis, we also assume that in many cases physicians’ estimates of adherence are based primarily on evaluation of treatment outcomes as indicated by clinical laboratory tests. Our findings also suggest that patient-experienced adherence can be low even though the clinical treatment response is optimal.

### 10.1.2 Patient-reported ADRs and their influence on medication adherence

As CML patients come to expect increasingly longer survival with TKI therapy, the importance of managing symptom burden related to the disease and its treatment will also increase. It has been reported in previous studies that symptom burden is cited as a primary reason for poor adherence to TKI therapy, while poor adherence has been linked to unsatisfactory treatment response and increased healthcare resource utilization (Noens et al. 2009, Marin et al. 2010, Eliasson et al. 2011).

Only 10% of the patients in the study (II) spontaneously reported ADRs had influenced their medication taking, i.e. they had stopped taking the medication or reduced the dose when feeling worse. Patients were willing to take the medication even though they were reporting ADRs. The complex interplay between symptom burden, adherence, response to TKI therapy, and healthcare utilization highlights the need for regular symptom burden assessment in CML as a means to identify potential adherence problems before they affect the patients’ response to TKI treatment. Information on the disease and treatment-related effects from the patient’s perspective crucially provides the additional knowledge needed for both patients and physicians to make informed treatment decisions. Many patients do not exhibit disease symptoms at diagnosis, and therefore may be irritated by the ADRs caused by the treatment.
10.1.3 Influence of ADRs on patients’ QoL

We were unable to find a clinical correlation between ADRs and patient non-adherence, but there was a significant correlation between higher number of symptoms and a negative impact on the patient’s QoL (II).

Results from previous randomized controlled trials suggest that treatment decisions influenced by QoL considerations may be beneficial in some patients (Hahn et al. 2003). It has been shown in previous studies that treatment with TKIs generally does not adversely affect – and may even improve – patient QoL (Basch et al. 2009). As stated by the FDA, some “treatment effects are known only to the patient” and such information can be lost when the patient’s perspective “is filtered through a clinician’s evaluation of the patient’s response to clinical interview questions” (FDA 2009). Thus it is likely that robust QoL evidence in this area will help physicians to make more tailored treatment decisions. In some therapeutic areas, symptom-specific rating scales have been found to be valuable tools for assessing the effects of an intervention on treatment-related symptoms. In general, patients report symptoms earlier and more frequently than clinicians. From these studies, it appears that clinicians may be better at recognizing ADRs with potentially serious consequences, whereas patients may be better at assessing more subtle changes that affect their overall QoL.

The emergence of treatment-related ADRs, although potentially detrimental to patient QoL, can be managed effectively in most cases because ADRs are mostly mild to moderate in severity and generally consistent (i.e. predictable) over time and across lines of therapy. Furthermore, the number of TKIs currently approved for the market increases the likelihood that patients found to be intolerant to one TKI can switch to another, better tolerated alternative.

10.1.4 Knowledge of the disease

In this study, knowledge of the disease and its treatment was poor irrespective of the adherence level (I, III). Few patients understood the consequences of not taking their medication. Understanding the treatment goals was seen as a motivating factor to adhere to the treatment. A real partnership between healthcare professionals and patients would help patients to better follow their treatment plans.

10.1.5 Reasons for non-adherence – qualitative analysis

It has been reported in previous studies that adherence to TKIs declines with time (Noens et al. 2009, Abraham et al. 2008). Our finding was the opposite: non-adherent patients in the study were more recently diagnosed than adherent ones (I-IV). Additionally, patients with suboptimal adherence were
younger, and therefore more often at work. We were not able to find a statistically significant correlation between non-adherence and gender, age, time from diagnosis, adverse effects, knowledge or education as published in many previous studies (Noens et al. 2009, Eliasson et al. 2011, Efficace et al. 2012a). However, the reasons for non-adherence were similar to those found in these other CML-related studies. Forgetting to take the medication was common. This is a human phenomenon, related to the fact that patients have so many other things in their lives competing for their time and attention than medication taking.

10.1.6 Patient journey

In this study we developed a patient journey model. The model, which is based on the experiences of CML patients with low adherence, helped to identify the critical phases in the CML patient’s journey, such as getting the diagnosis, starting the treatment, getting continuous support for self-management of the treatment, and managing with the fear caused by the perceived severity of the disease. This is unique and provides further knowledge of the factors contributing to low adherence. This kind of integrated understanding is needed to influence the system-based factors that prevent low adherence from occurring with TKI treatment. The first crucial step in the CML patients’ journey was found to be getting the diagnosis. This represented a crisis for all patients with low adherence and is in line with the study by Guilhot et al. (2013). More attention should be paid to the way patients are told of the diagnosis and how they are emotionally supported to cope with the shocking, unexpected news, as quite a number of the study participants criticized the current way of doing it. In many cases the patient was informed of the diagnosis by phone and then invited to come to the hospital for the start of treatment. This increased their negative emotional load. Also, the information provided at the time of diagnosis was insufficient. This concerned not only the disease and its treatment, but the available support services, such as psychologists and social workers. It seems that for many patients non-adherence could be prevented by supporting them at the very beginning of their journey: give them more psychological support, involve them in the treatment and its goals, and provide them with written treatment plans and medication lists. It is important to build a bridge between the healthcare system and patients taking their medicines at home and to ensure the continuity of support throughout the journey.

10.1.7 Impact of the educational intervention on adherence

The patients with CML involved in the study did not regard text message reminders to be as important as other adherence aids (IV). Many previous studies have shown positive results with text messages as sole adherence aid
As those studies have not compared different adherence aids nor assessed patients’ preferences, they do not provide comparative evidence of the perceived usefulness of the various adherence aids. It is important to understand and consider patients’ perceptions and preferences when designing patient education interventions for real-life clinical practice. Otherwise, adherence aids may favor, say, electronic reminders, whereas patients want to meet their nurse or other healthcare provider.

The top three patient information priorities found in a systematic review of thirty studies involving patients with different cancers were related to 1) prognosis, 2) diagnosis, and 3) treatment options (Tariman et al. 2014). The authors suggest these topics could serve as a start to elicit CML patients’ information needs and guide patient education across the patient journey. Being able to prioritize the most-needed information can make patient encounters more meaningful and useful (Tariman et al. 2014). Patients in the present study were willing to take their medication, but unfortunately the system-related factors/tools (written treatment plan, medication list) used to support self-management and medicine taking at home were lacking in all cases (I, III). Their non-adherence could be at least partly prevented by better involving them in the treatment and its goals with written treatment plans and medication lists.

10.2 Methodological considerations

10.2.1 Study participants

This study involves insights into the journey of 86 CML patients taking TKIs. As the patients come from eight hospitals operating in different parts of Finland the study provides quite a good overview on the quality of CML care from the patients’ perspective in Finland. The study participants represented 20% of all Finnish CML patients and involved 13 physicians specializing in CML care.

Due to the possibility of biasing factors our results do not necessarily reflect the complete picture of TKI adherence in Finland. There may have been more non-adherent patients declining to participate during the study enrolment period, thus resulting in increased selection bias. However, the highly standardized data gathering procedure and personal interviews conducted by one person meant there was no inter-observer bias. On the other hand, the method used to obtain physicians’ subjective assessments of their patients’ adherence is not well standardized and includes the risk of inter-observation bias. In clinical practice, however, the high risk of a subjective overestimation of TKI adherence in individual patients is more relevant.
Because of the large amount of transcription data (86 patients), the qualitative analysis was intentionally focused on those patients with low adherence to their TKI treatment (n=18). Thus, the present study provides no evidence on how patients with higher adherence scores differed in their experiences and behaviors from those with low adherence scores as measured by MMAS.

10.2.2 MMAS

The 8-Item MMAS shows three different adherence rates (Morisky at al. 2008). Patients with the rating 2 or 3 (medium or low) are not ‘fully’ adherent. In our study this represented 77% of the patients (I-IV). The patient needs to score all eight points to be highly adherent according to MMAS. This might influence the results. MMAS has not been specially developed for the evaluation of medication adherence in CML patients, although it is widely used in other chronic illnesses. It would be interesting to validate a CML-specific adherence scale in the future. Almost all of the physicians’ assessments were ‘high adherence’, which caused bias in the comparison between experienced and observed adherence (I). We were therefore unable to perform any statistical analysis between these two assessments. This should be addressed in future studies.

10.2.3 Theme interviews

A semi-structured interview method with pre-defined key topics and themes was used (I-IV). The interviews were conducted using a flexible structure, which allowed conversational, two-way communication between interviewer and interviewee (Mason 2004). All the patients participated in two in-person interviews with the same investigator (MK) (baseline and at nine months), which is a unique approach. The interviews were audiotaped and transcribed verbatim by a professional transcriber.

10.2.4 Intervention

As the adherence rate was the same in the intervention and control groups at baseline, it was possible to observe whether the adherence rate improved with enhanced support or declined without it over the 9-month period (IV). It was evident that the adherence rate tended to decline without support. This indicates that patients with CML on long-term therapies need continuous support to retain their motivation to regularly take their medication.

Because few published studies have addressed adherence improvement techniques in patients with cancer, methods described for the general population in previous studies have been extrapolated for this group of
patients (McCue et al. 2014). Patient education interventions, including a combination of face-to-face counseling and interactive technologies or videos, have proved to be the most effective (Gysels et al. 2004). For this reason patient education in the present study was designed as an entity made up of different empowering adherence aids supporting patient self-management and creation of a partnership with nurses.

Crucial aspects for the scientific rigor of Study IV were 1) the controlled study design with an appropriate number of participants randomly allocated to the study group and control group, 2) carefully planned educational intervention applying a relevant combination of adherence aids, 3) standardization of the delivery of the intervention in all eight hospitals involved in the study by training the nurses and providing them with the same resources for patient education, 4) having a follow-up period long enough to measure the impact of the intervention on medication adherence, and 5) applying a validated quantitative measure for adherence assessment completed during qualitative patient interviews to assure face-validity and high participation rate. As the data sets were complete for each patient, 6) we did not need to make adjustments in the data analysis for missing data, 7) all data was collected by one author (MK) in order to standardize the data collection procedure. And finally, 8) nurses who delivered the intervention did not meet patients allocated to the control group (standard treatment) in order to avoid dilution of results.

10.2.5 ADR and QoL assessment

The study was cross-sectional (patient interviews conducted at baseline) (II). ADRs were only reported by the patient and not compared with the physician’s assessment.

The instruments used for assessing ADRs and QoL were not validated (II). At the time this study was started, no validated QoL assessment instruments specific to leukemia or CML were available. Recently however, three leukemia- and CML-specific QoL instruments have been validated: the FACT-Leu (Trask et al. 2013), the MDASI-CML (Williams et al. 2013) and the EORTC QLQ-CML (Efficace et al. 2014a). The further development and validation of leukemia- or CML-specific QoL measurement tools could improve the overall management of CML.
11 Practical Implications

11.1 Implications for further research and evaluation

CML has changed from a fatal to a chronic disease during the last decade. Nowadays the patient is fully responsible for managing the treatment at home. This change presumes a new type of co-operation and partnership between the physician and the patient. The physician is the medical expert when it comes to the illness and its medication, while the patient best understands his/her everyday life with the disease and its treatment. It is important to understand the root causes of patients’ non-adherence in order to encourage them to take responsibility for their own treatment. Further research is needed to understand these changes in the medication management processes of CML patients arising from current advances in pharmacotherapies.

Controlled studies assessing adherence over time with repeated measurements are needed to provide a better understanding of adherence behavior and its changes. Additionally, identifying risk factors for clinically significant declines in adherence will allow effectively targeted interventions to maintain high adherence and avoid the adverse consequences of poor adherence. It would be interesting to evaluate the severity of the symptoms in future studies.

Future studies should apply methods and study designs that will provide more comparative evidence on the effectiveness of different kinds of adherence aids from the patient’s perspective.

11.2 Implications for healthcare services

As demonstrated in this thesis, sub-optimal adherence to TKI therapy in CML is a widespread problem that may compromise treatment outcomes. Physicians and healthcare professionals have a key role to play in promoting adherence among patients through assessment, communication, education and personalized solutions.

The findings of the intervention study (IV) have implications for the training of nurses and other healthcare providers, as well as for organizing patient education and adherence support as an essential part of patient care. More should be done to involve patients in the planning of adherence support and in applying different adherence aids, even the most innovative digital ones. Organizational development is needed as well, so that patient education and adherence support can be integrated into standard care.

Simple measurement tools such as MMAS might be helpful in identifying some of the adherence problems in clinical practice. MMAS is a short and easily used
tool applicable to routine practice. In this study MMAS questions were asked verbally in interviews (I-IV). We suggest that this approach can give more information than asking the patient to fill in a form. More important than the numeric value of adherence is the information that the eight items provide about medicine use. The MMAS's eight items indicate intentional and unintentional reasons for non-adherence and could help physicians and nurses to evaluate adherence, identify adherence problems and discuss them with the patient. It is important to train physicians and other healthcare providers about adherence and its role in managing medication use in clinical practice.

The ADRs that had the most negative effect on patients’ QoL in the present study were swelling, rashes, disturbed sleep, feeling sad or depressed, problems remembering things and a feeling of malaise (II). Identifying these symptoms could help in treatment follow-up designed to manage ADRs and to help patients to continue their treatment successfully. Good QoL is necessary to support the proper use of TKI therapy in CML.

Intentional self-regulation of medicine taking seemed to be related to managing ADRs in situations where they would have prevented normal life, e.g. participation in social events (III). It is important to educate patients to know the limits of self-regulation as it is part of the journey: how many doses can be skipped and how often without jeopardizing treatment outcomes. This kind of communication to improve the patient’s ability to follow the treatment plan throughout the journey requires a real partnership between healthcare professionals and the patient.

The patient journey model developed in this study helped to identify the critical phases in the CML patient’s journey and provides further knowledge of the factors contributing to low adherence (III). This kind of integrated understanding is needed to influence the system-based factors that prevent poor adherence from occurring with TKI treatment.

It seems that for many patients non-adherence could be prevented by supporting them at the very beginning of their journey: give them more psychological support, involve them in the treatment and its goals, and provide them with written treatment plans and medication lists (I, III). These simple tools could also increase patients’ knowledge of CML as a disease and its treatment, which was found to be poor in our study. Solving these medication management-related issues may require physicians to be more aware of a range of factors related to adherence and self-management of long-term diseases, such as CML, requiring patients’ active involvement. It is important to build a bridge between the healthcare system and patients taking their medicines at home and to ensure the continuity of support throughout the journey.

Our findings indicate that access to personal counseling and information should be systematically planned as an essential part of CML care (IV). Each patient with CML should have a customized support plan based on their
special needs. These tailored support plans should recognize that the need for support varies in different phases of the disease and between patients (Ryan et al. 2014). To achieve these goals in practice requires healthcare providers involved in CML care to be capable of creating a therapeutic alliance with their patients so that the patients can develop the problem-solving skills needed in the self-management of CML with TKIs. Another requirement is the availability of appropriate and updated information in printed and electronic formats.

Successful pharmacotherapy requires communication and planned collaboration between physicians, nurses, pharmacists and patients. It is therefore important to combine different types of adherence aids, such as those used in the present study, and to train healthcare providers in adherence and its role in managing medication use in clinical practice (IV). The patient journey model might also help in identifying each patient’s personal needs (III).
12 Conclusions

This study found that patient-reported adherence to TKI treatments in Finland is the same as that found in the majority of previous studies, 21% having low adherence as measured by MMAS. However, there seems to be a very weak agreement between the patient’s and the physician’s assessment of adherence, physicians having a tendency to overestimate adherence in CML patients. This may be related to the finding that physicians based their adherence estimation primarily on the patients’ clinical treatment response. Despite a good clinical response, patients may lack knowledge of CML as a disease and its treatment with TKIs, as well as access to a treatment plan and medication list (I).

TKI-related ADRs were common among CML patients irrespective of medication adherence level. Patients who reported that ADRs had a negative influence on their daily QoL experienced more ADRs than those who did not report a negative influence (II).

The patient journey model developed in this study helped to identify critical phases in the CML patient’s journey influencing adherence, the first of them being getting the diagnosis. It is important to educate patients about self-regulating their TKI medication, including managing ADRs, as self-regulation is part of their journey and a contributor to non-adherence. Communication to improve patients’ ability to follow their treatment plan throughout the journey requires a real partnership between healthcare professionals and patients (III).

Tailored patient education improved the medication adherence of patients with CML. Without this support, adherence behavior tended to decline. Personal communication with a nurse proved to be an essential part of adherence support and should not be ignored despite the growing number of digital adherence aids. It is important to understand and consider patient perceptions and preferences when designing patient education interventions for real-life clinical practice in the future (IV).
13 References


De Almeida MH, Barbosa Pagnano KB, Sanches Souza HA, Souza CA: Adherence to tyrosine kinase inhibitors (TKI) in chronic myeloid leukemia (CML) seems to be related to duration of treatment and type of TKI. Haematologica 95 (Suppl. 2), 2010.


Bennett JH: Case of hypertrophy of the spleen and liver in which death took place from suppuration of the blood. Edinb Med Surg J 64:413–423, 1845.


Bosulif SPC, 2015.


Casamartina EF et al.: Study of variability in the response to imatinib treatment in Chronic Myeloid Leukemia Ph+ patients. J Oncol Pharm Pract 16 (Suppl. 1)9, 2010.


Glivec (imatinib) SPC East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.


Iclusig SPC Ariad Pharma (UK) Ltd, 2015.


Kela, personal information, 2016.


Tasigna (nilotinib) SPC East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.


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